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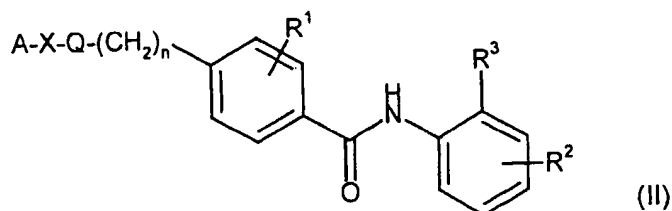
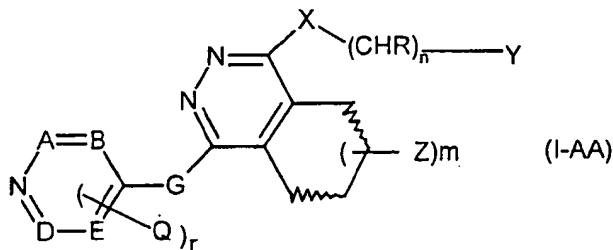
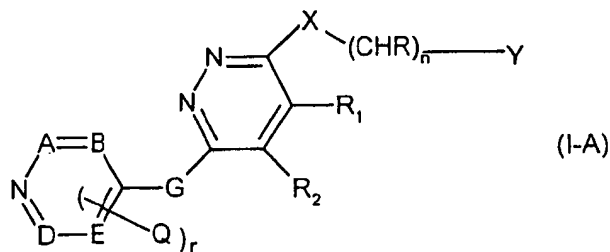
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[Continued on next page]

(54) Title: PHARMACEUTICAL COMBINATIONS OF PHTHALAZINE VEGF INHIBITORS AND BENZAMIDE HDAC INHIBITORS



(57) Abstract: Pharmaceutical combinations comprising at least one compound of general formula I-A or I-AA, and at least one compound of general formula II) or IIa), or pharmaceutical combinations comprising at least one compound of general formula I-A or I-AA, and at least one compound of general formula II) or IIa), and an anti-hormone, and their use for the treatment of different diseases resulting by persistent angiogenesis are described.



SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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New Pharmaceutical Combination

The invention concerns pharmaceutical combination and their use for the treatment of diseases resulting from persistent angiogenesis.

5

Persistent angiogenesis can be the source for different diseases, such as for example psoriasis, arthritis, such as rheumatoid arthritis, haemeangioma, angiofibroma, diseases of the eyes, such as diabetic retinopathie, neovascular glaucoma, diseases of the kidney, such as glomerulonephritis, diabetic

10 nephropatic disease, malignant nephrosclerosis, thrombotic microangiopathic syndrome, disposes of transplants and glomerulopathy, fibrotic diseases, such as liver cirrhosis, mesangial cell proliferative diseases and arteriosclerosis, or can be change for the worse of these diseases.

15 A direct or indirect inhibition of the VEGF-receptor can be used for the treatment of the described diseases and other VEGF-induced pathological angiogenesis and vascular permeable conditions, such as tumor vasculature.

For example, it is known that the growth of a tumor can be inhibited by soluble receptors and antibodies against VEGF.

20

Persistent angiogenesis can be induced by VEGF via its receptor. For this, it is necessary that VEGF binds to the receptor and a tyrosine phosphorylation is achieved.

25 Compelling data implicate angiogenesis and tumor-associated neovascularization as a central step in the process of tumor growth, invasion, and metastasis. Angiogenesis involves multiple steps and pathways dependent on the local balance between positive and negative regulatory factors, as well as interactions among the tumor, its vasculature, and the surrounding

30 extracellular tissue matrix. A tumor remains in a dormant state, where the cellular proliferation rate is balanced by the apoptotic rate, and it is unable to grow in size beyond a few millimeters if it has not acquired an angiogenic

phenotype.

VEGF-A, an endothelial cell specific mitogen, is considered to play a key role in angiogenic processes apparent in tumor growth. It has been shown to be
5 secreted by hypoxic cells and cells of the reproductive apparatus under the regulation of oxygen partial pressure or hormones. VEGF has a variety of effects on vascular endothelium, including the ability to promote endothelial cell viability, mitogenesis, chemotaxis, and vascular permeability. It mediates its activity mainly via two tyrosine kinase receptors, VEGFR-1 (flt-1) and VEGFR-2
10 (flk-1/KDR), although other receptors, such as neuropilin-1 and -2, can also bind VEGF-A.

Inhibition of VEGF-induced angiogenic signals will selectively target tumor-associated vessels, since cell division of endothelial cells in the normal vasculature is a very rare event and those cells are in a stabilized environment
15 *with pericytes and smooth muscle cells that render them stable in the absence of VEGF. Therefore, antiangiogenic therapy through inhibition of VEGF-mediated effects, is expected to be safe and well tolerated in cancer patients.*
VEGF-A is also a potent inducer of vascular permeability (second name: vascular permeability factor, VPF) and may also play a key role in ascitic fluid
20 *formation and oedema associated with malignant disease. Two VEGF-analogs, VEGF-C and VEGF-D have been described that bind to VEGFR-2 and VEGFR-3. The latter receptor appears to be responsible for lymphangiogenesis and may play a role in lymphogenic metastasis.*

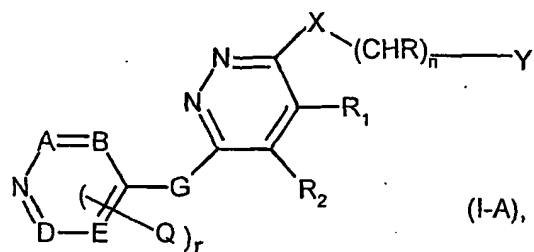
A VEGF signal inhibitor will not directly inhibit tumor cell growth. It will influence
25 *tumor growth by inhibiting tumor vascularization. It needs a constant long term application to exert its efficacy. The desired compound should therefore not cause major adverse effects that compromise the patients quality of life.*

VEGF signal inhibitors are intended for a continuous long lasting therapy. It is
30 *clear that VEGF signal inhibitors are much better tolerated than conventional cytotoxic antitumor agents if they are specific.*

VEGF signal inhibitors will interfere with important physiological processes

(wound healing, menstrual cycle, pregnancy, fetal development) which may impose treatment interruptions and restrictions of indications. At present, none of these questions appears to compromise patient treatment. This is due to the fact that the majority of patients passed the reproductive age. Healing of small wounds might be regulated through other pathways like FGF signaling. From animal experiments and from treatments of patients it is known that potential effects on hematopoietic and other stem cells that express VEGFR did not materialize in changes of blood cell composition. VEGFR occurring in glomeruli of the kidney and in one cell layer near the chorioid plexus did not react with recognizable functional deficits on kinase blockade.

In WO 98/35958 phthalazine derivatives are described which show angiogenesis inhibiting activity. These compounds of the general structure I-A



wherein

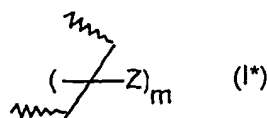
r is 0 to 2,

n is 0 to 2,

m is 0 to 4,

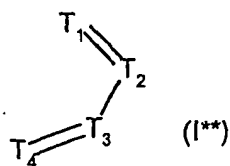
R₁ and R₂ (i) are lower alkyl or

(ii) together form a bridge in subformula I*



the binding being achieved via the two terminal carbon atoms, or

(iii) together form a bridge in subformula I**



5

wherein one or two of the ring members T_1 , T_2 , T_3 and T_4 can be nitrogen, and the others are in each case CH, and the binding is achieved via T_1 and T_4

10

A, B, D and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N;

G is lower alkylene, lower alkylene substituted by acyloxy or hydroxy, $-\text{CH}_2\text{-O-}$, $\text{CH}_2\text{-S-}$, $-\text{CH}_2\text{-NH-}$, oxa ($-\text{O-}$), thia ($-\text{S-}$), or imino ($-\text{NH-}$);

15

Q is lower alkyl;

R is H or lower alkyl;

X is imino, oxa, or thia;

20

Y is unsubstituted or substituted aryl, pyridyl, or cycloalkyl; and

25

Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N, N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or alkylphenylsulfinyl, substituents Z being the same or different from one another if more than 1 radical Z is present;

30

and wherein the bonds characterized, if present, by a wavy line are either single or double bonds;

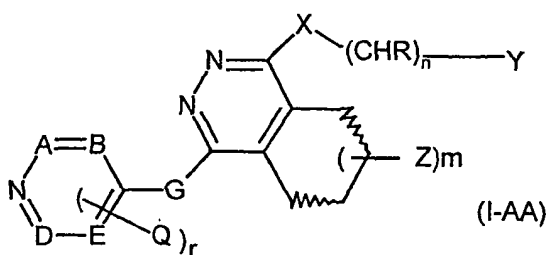
or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom;

- 5 with the stipulation that, if Y is pyridyl or unsubstituted cycloalkyl, X is imino, and the remaining radicals are as defined, G is selected from the group comprising lower alkylene, $-\text{CH}_2\text{-O-}$, $-\text{CH}_2\text{-S-}$, oxa and thia; or a salt thereof, are of interest as compound A) of the inventive synergistic combination.

10

Also those compounds which are described in WO 98/35958 are useful for the synergistic combination, which have the structure of general formula I-AA

15



20 wherein

r is 0 to 2,

n is 0 to 2,

m is 0 to 4,

25 A, B, D and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N;

G is lower alkylene, $-\text{CH}_2\text{-O-}$, $-\text{CH}_2\text{-S-}$, $\text{CH}_2\text{-NH-}$, oxa, thia, or imino;

30 Q is methyl;

R is H or lower alkyl;

X is imino, oxa, or thia;

Y is unsubstituted or substituted aryl, pyridyl, or cycloalkyl; and

5

Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or alkylphenylsulfinyl, substituents Z being the same or different from one another if more than 1 radical Z is present;

10

and wherein the bonds characterized by a wavy line are either single or double bonds;

15

or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom;

with the stipulation that, if Y is pyridyl or unsubstituted cycloalkyl, X is imino, and the remaining radicals are as defined, G is selected from the group comprising lower alkylene, -CH₂-O-, -CH₂-S-, oxa and thia; or a salt thereof.

20

Of special interest for the inventive combination are those compounds of general formula I-AA, wherein

25

r is 0 to 2,

n is 0 or 1,

m is 0 or 1,

30 A, B, D and E are in each case CH,

G is lower alkylene, especially methylene,

Q is methyl, which is bound to A, to D, or to A and D;

R is H or lower alkyl,

5

X is imino,

Y is phenyl, which is unsubstituted or substituted by one or two substituents independently of one another from the group comprising amino; lower

10 alkanoylamino; halogen; lower alkyl; halogen-lower alkyl; hydroxy; lower alkoxy; phenyl-lower alkoxy; and cyano, or is pyridyl;

Z is amino; N-lower alkylamino; hydroxy-lower alkylamino; phenyl-lower alkylamino; N, N-di-lower alkylamino; n-phenyl-lower alkyl-N-lower alkylamino; 15 N,N-di-lower alkylphenylamino; lower alkanoylamino; or a substituent from the group comprising benzoylamino or phenyl-lower alkoxycarbonylamino, wherein the phenyl radical in each case is unsubstituted or especially substituted by nitro or amino, or by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, lower alkanoyl or 20 carbamoyl; or is halogen; and,

the bonds characterized by a wavy line are in each case a double bond or in each case a single bond; or a salt thereof.

25 Also of special interest for the inventive synergistic combination are those compounds of general formula I-A, wherein

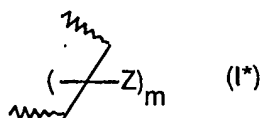
r is 0 to 2,

n is 0 or 1,

30 m is 0 or 1,

R₁ and R₂ (i) are lower alkyl or

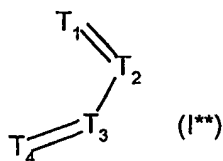
(ii) together form a bridge in subformula l^*



5

the binding being achieved via the two terminal carbon atoms, or

- (iii) together form a bridge in subformula l^{**}



10

wherein one of the ring members T₁, T₂, T₃ and T₄ can be nitrogen, and the others are in each case CH, and the binding is achieved via T₁ and T₄

15 A, B, D and E are in each case CH, or A, D and E are each CH and B is N;

G is lower alkylene, -CH₂-NH-, -CH₂-O-, hydroxymethylene, or benzoyloxymethylene,

20 Q is methyl, which is bound to A, to D, or to A and D;

R is H or lower alkyl,

X is imino, oxa, or thia,

25

Y is phenyl, which is unsubstituted or is substituted by one or two substituents independently of one another from the group comprising amino; lower alkanoylamino; halogen, lower alkyl; halogen-lower alkyl; hydroxy; lower alkoxy; phenyl-lower alkoxy; cyano; benzyloxy; lower alkenyl, C₈-C₁₂ alkoxy, lower alkoxycarbonyl, carbamoyl lower alkylcarbamoyl, lower alkanoyl, phenyloxy, halogen-lower alkyloxy, lower alkoxycarbonyl, lower alkylmercapto, halogen-lower alkylmercapto, hydroxy-lower alkyl, lower alkylsulfonyl, halogen-lower

alkylsulfonyl, phenylsulfonyl, dihydroxybora, 2-methylpyrimidin-4-yl, oxazol-5-yl, 2-methyl-1,3-dioxolan-2-yl, 1H-pyrazol-3-yl, 1-methylpyrazol-3-yl, and lower alkylenedioxy bound to two adjacent C atoms, or is also pyridyl;

5 Z is amino; N-lower alkylamino; hydroxy-lower alkylamino; phenyl-lower alkylamino; N, N-di-lower alkylamino; n-phenyl-lower alkyl-N-lower alkylamino, N,N-di-lower alkylphenylamino; lower alkanoylamino; or a substituent from the group comprising benzoylamino or phenyl-lower alkoxycaarbonylamino, wherein the phenyl radical in each case is unsubstituted or substituted by nitro
10 or amino, or by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, lower alkanoyl or carbamoyl; or is halogen; and, if present (in formula IA), the bonds characterized by a wavy line are in each case a double bond or in each case a single bond; or a salt thereof.

15

Of most interest for the inventive synergistic combination are those compounds of general formula I-AA, wherein

r is 0,

20 n is 0 or 1,

m is 0;

A, B, D and E are in each case CH,

25 G is lower alkylene,

R is H;

X is imino,

30

Y is phenyl, which is unsubstituted or substituted by one or two substituents independently of one another from the group comprising amino; lower

alkanoylamino; halogen; lower alkyl; halogen-lower alkyl; hydroxy; lower alkoxy; phenyl-lower alkoxy; and cyano; and

the bonds characterized by a wavy line are double bonds; or a salt thereof.

5

Also of special interest for the inventive synergistic combination are those compounds of general formula I-AA, wherein

r is 0,

n is 0 or 1,

10 m is 0;

A, B, D, and E are in each case CH,

G is methylene,

15 R is H,

X is imino,

Y is phenyl, 2-, 3- or 4-aminophenyl, 2-, 3- or 4-acetylamino-phenyl, 2-, 3- or 4-
20 fluorophenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2,3-, 2,4-, 2,5- or
3,4-dichlorophenyl, chlorofluorophenyl, 2-, 3- or 4-methylphenyl, 2-, 3- or 4-
trifluoromethylphenyl, 2-, 3- or 4- hydroxyphenyl, 2-, 3- or 4- methoxycarbonyl,
methoxychlorophenyl, 2-, 3- or 4- benzyloxyphenyl, or 2-, 3- or 4-cyanophenyl;
and

25

the bonds characterized by the wavy line are double bonds; or a salt thereof.

Selected compounds for the inventive combination are

30 1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine,
1-(4- Methylanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Chloroanilino)-4-(4-pyridylmethyl)phthalazine;

- 1-Anilino-4-(4-pyridylmethyl)phthalazine;
1-Benzylamino-4-(4-pyridylmethyl)phthalazine;
1-(4-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Benzoyloxyanilino)-4-(4-pyridylmethyl)phthalazine;
5 1-(3-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(2-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Trifluoromethylanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Fluoroanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Hydroxyanilino)-4-(4-pyridylmethyl)phthalazine;
10 1-(4-Hydroxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Aminoanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3,4-Dichloroanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Bromoanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Chloro-4-methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
15 1-(4-Cyanoanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Chloro-4-fluoroanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Methylanilino)-4-(4-pyridylmethyl)phthalazine; or in each case a
pharmaceutically acceptable salt thereof.
- 20 If G is a bivalent group $-\text{CH}_2\text{-O-}$, $-\text{CH}_2\text{-S-}$, or $-\text{CH}_2\text{-NH-}$, the methylene group in
each case is bound to the ring with ring members A, B, D, and E, whereas the
heteroatom (O, S or NH) is bound to the phthalazine ring in formula I-A.
- Lower alkylene G may be branched or preferably linear and is especially
25 branched or preferably linear $\text{C}_1\text{-C}_4$ alkylene, especially methylene ($-\text{CH}_2-$),
ethylene ($-\text{CH}_2\text{-CH}_2-$), trimethylene ($-\text{CH}_2\text{-CH}_2\text{-CH}_2-$) or tetramethylene ($-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2-$). G is preferably methylene.
- Acyl in lower alkylene substituted by acyloxy is preferably arylcarbonyloxy,
30 wherein aryl is defined as below, especially benzoyloxy or lower alkanoyloxy,
especially benzoyloxy; lower alkylene substituted by acyloxy is especially
methylene substituted by benzoyloxy.

Lower alkylene substituted by hydroxy is preferably hydroxymethylene (-CH(OH)-).

- 5 G as lower alkylene substituted by acyloxy or hydroxy is preferred, or G as otherwise defined hereinbefore and hereinafter is in each case especially preferred.

- 10 Q is preferably bound to A or D ($r = 1$) or to both ($r = 2$), where in the event of binding of Q, A and/or D are/is C(-Q).

Lower alkyl is especially C₁-C₄alkyl, e.g. n-butyl, sec-butyl, tert-butyl, n-propyl, isopropyl, or especially methyl or also ethyl.

- 15 In the preferred embodiment, aryl is an aromatic radical having 6 to 14 carbon atoms, especially phenyl, naphthyl, fluorenyl or phenanthrenyl, the radicals defined above being unsubstituted or substituted by one or more, preferably up to three, especially one or two substituents, especially selected from animo, mono-or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, 20 alkanoyl, carbamoyl, N-mono-or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfinyl, phenyl-lower alkylsulfinyl, alkylphenylsulfinyl, phenylsulfonyl, phenyl-lower alkylsulfonyl, and alkylphenylsulfonyl, or (as an alternative or in 25 addition to the above group of substituents) selected from lower alkenyl, such as ethenyl, phenyl, lower alkylthio, such as methylthio, lower alkanoyl, such as acetyl, lower alkylmercapto, such as methylmercapto (-S-CH₃), halogen-lower alkylmercapto, such as trifluoromethylmercapto (-S-CF₃), lower alkylsulfonyl, halogen-lower alkylsulfonyl, such as especially trifluoromethane sulfonyl, 30 dihydroxybora (-B(OH)₂), heterocyclyl, and lower alkylene dioxy bound at adjacent C-atoms of the ring, such as methylene dioxy; aryl is preferably phenyl which is either unsubstituted or independently substituted by one or two

substituents selected from the group comprising amino; lower alkanoylamino, especially acetylamino; halogen, especially fluorine, chlorine, or bromine; lower alkyl, especially methyl or also ethyl or propyl, halogen-lower alkyl, especially trifluoromethyl; hydroxy; lower alkoxy, especially methoxy or also ethoxy;

5 phenyl-lower alkoxy, especially benzyloxy; and cyano, or (as an alternative or in addition to the previous group of substituents) C₈-C₁₂alkoxy, especially n-decyloxy, carbamoyl, lower alkylcarbamoyl, such as n-methyl- or n-tert-butylcarbamoyl, lower alkanoyl, such as acetyl, phenyloxy, halogen-lower alkyloxy, such as trifluoromethoxy or 1,1,2,2-tetrafluoroethyloxy, lower

10 alkoxycarbonyl, such as ethoxycarbonyl, lower alkylmercapto, such as methylmercapto, halogen-lower alkylmercapto, such as trifluoromethylmercapto, hydroxy-lower alkyl, such as hydroxymethyl or 1-hydroxymethyl, lower alkylsulfonyl, such as methan sulfonyl, halogen lower alkylsulfonyl, such as trifluoromethane sulfonyl, phenylsulfonyl, dihydroxybora (-B(OH)₂), 2-

15 methylpyrimidin-4-yl, oxazol-5-yl, 2-methyl-1,3-dioxolan-2-yl, 1H-pyrazol-3-yl, 1-methyl-pyrazol-3-yl and lower alkylene dioxy bound to two adjacent C-atoms, such as methylene dioxy.

Where mention is made hereinbefore and hereinafter to radicals or substituents

20 as „an alternative or in addition to“ the previous group of radicals or substituents, these radicals or substituents and those of the previous group are to be regarded together as one group of substituents from which the respective radicals may be selected, or especially as separate groups. The expression

does not mean that one of the radicals following the expression may be added

25 to a member of the previous group by binding. This applies, even if the expression „as an alternative or in addition to“ is not mentioned again, for the radicals or substituents, as defined here, in the preferred compounds of formula I defined below.

30 Mono-or disubstituted amino is especially amino substituted by one or two radicals selected independently of one another from lower alkyl, such as methyl; hydroxy-lower alkyl, such as 2-hydroxyethyl; phenyl-lower alkyl; lower alkanoyl,

such as acetyl; benzoyl; substituted benzoyl, wherein the phenyl radical is unsubstituted or especially substituted by one or more, preferably one or two, substituents selected from nitro or amino, or also from halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, lower alkanoyl, and carbamoyl; and phenyl-lower alkoxy carbonyl, wherein the phenyl radical is unsubstituted or especially substituted by one or more, preferably one or two, substituents selected from nitro or amino, or also from halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, lower alkanoyl, and carbamoyl; and is preferably N-lower alkylamino, such as N-methylamino, hydroxy-lower alkylamino, such as 2-hydroxyethylamino, phenyl-lower alkylamino, such as benzylamino, N,N-di-lower alkylamino, N-phenyl-lower alkyl-N-lower alkylamino, N,N-di-lower alkylphenylamino, lower alkanoylamino, such as acetylamino, or a substituent selected from the group comprising benzoylamino and phenyl-lower alkoxy carbonylamino, wherein the phenyl radical in each case is unsubstituted or especially substituted by nitro or amino, or also by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, lower alkanoyl or carbamoyl, or as an alternative or in addition to the previous group of radicals by aminocarbonylamino.

Halogen is especially fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

In the preferred embodiment, alkyl has up to a maximum of 12 carbon atoms and is especially lower alkyl, especially methyl, or also ethyl, n-propyl, isopropyl, or tert butyl.

Substituted alkyl is alkyl as last defined, especially lower alkyl, preferably methyl; where one or more, especially up to three, substituents may be present, primarily from the group selected from halogen, especially fluorine, and also

from amino, N-lower alkylamino, N,N-di-loweralkylamino, N-lower alkanoylamino, hydroxy, cyano, carboxy, lower alkoxycarbonyl, and phenyl-lower alkoxycarbonyl. Trifluoromethyl is especially preferred.

- 5 Etherified hydroxy is especially C₈-C₂₀alkyloxy, such as n-decyloxy, lower alkoxy (preferred), such as methoxy, ethoxy, isopropoxy, or n-pentyloxy, phenyl-lower alkoxy, such as benzyloxy, or also phenyloxy, or as an alternative or in addition to the previous group C₈-C₂₀alkyloxy, such as n-decyloxy, halogen-lower alkoxy, such as trifluoromethyloxy or 1,1,2,2-tetrafluoroethoxy.

10

Esterified hydroxy is especially lower alkanoyloxy, benzoyloxy, lower alkoxycarbonyloxy, such as tert-butoxycarbonyloxy, or phenyl-lower alkoxycarbonyloxy, such as benzyloxycarbonyloxy.

- 15 Esterified carboxy is especially lower alkoxycarbonyl, such as tert-butoxycarbonyl or ethoxycarbonyl, phenyl-lower alkoxycarbonyl, or phenyloxycarbonyl.

Alkanoyl is primarily alkylcarbonyl, especially lower alkanoyl, e.g. acetyl.

20

N-mono- or N,N-disubstituted carbamoyl is especially substituted by one or two substituents, lower alkyl, phenyl-lower alkyl, or hydroxy-lower alkyl, at the terminal nitrogen atom.

- 25 Alkylphenylthio is especially lower alkylphenylthio.

Alkylphenylsulfinyl is especially lower alkylphenylsulfinyl.

Pyridyl Y is preferably 3- or 4-pyridyl.

30

Z is preferably amino, hydroxy-lower alkylamino, such as 2-hydroxyethylamino, lower alkanoylamino, such as acetylamino, nitrobenzoylamino, such as 3-

nitrobenzoylamino, aminobenzoylamino, such as 4-aminobenzoylamino, phenyl-lower alkoxy carbonylamino, such as benzyloxycarbonylamino, or halogen, such as bromine; preferably only one substituent is present ($m = 1$), especially one of the last mentioned, especially halogen. A compound of
5 formula I (or an N-oxide thereof), wherein Z is absent ($m = 0$), is quite especially preferred.

Unsubstituted or substituted cycloalkyl is preferably C_3 - C_8 cycloalkyl, which is unsubstituted or substituted in the same way as aryl, especially as defined for
10 phenyl. Cyclohexyl or also cyclopentyl or cyclopropyl are preferred.

Heterocyclyl is especially a five or six-membered heterocyclic system with 1 or 2 heteroatoms selected from the group comprising nitrogen, oxygen, and sulfur, which may be unsaturated or wholly or partly saturated, and is unsubstituted or
15 substituted especially by lower alkyl, such as methyl; a radical selected from 2-methylpyrimidin-4-yl, oxazol-5-yl, 2-methyl-1,3-dioxolan-2-yl, 1H-pyrazol-3-yl, and 1-methyl-pyrazol-3-yl is preferred.

Aryl in the form of phenyl which is substituted by lower alkylene dioxy bound to
20 two adjacent C-atoms, such as methylenedioxy, is preferably 3,4-methylenedioxyphenyl.

The bonds in formula I characterized by wavy lines are present either as single or as double bonds. Preferably both are at the same time either single or double
25 bonds.

An N-oxide of a compound of formula I is preferably an N-oxide in which a phthalazine-ring nitrogen or a nitrogen in the ring with ring members A, B, D, and E carries an oxygen atom, or several of the said nitrogen atoms carry an
30 oxygen atom.

Salts are especially the pharmaceutically acceptable salts of compounds of

formula I (or an N-oxide thereof).

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I (or an N-oxide thereof) with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid.

Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2-hydroxybutyric acid, gluconic acid, glucosemonocarboxylic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids, such as glutamic acid, aspartic acid, N-methylglycine, acetylminoacetic acid, N-acetylasparagine or N-acetylcysteine, pyruvic acid, acetoacetic acid, phosphoserine, 2- or 3-glycerophosphoric acid, glucose-6-phosphoric acid, glucose-1-phosphoric acid, fructose-1,6-bisphosphoric acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 1- or 3-hydroxynaphthyl-2-carboxylic acid, 3,4,5-trimethoxybenzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, glucuronic acid, galacturonic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

In the presence of negatively charged radicals, such as carboxy or sulfo, salts may also be formed with bases, e.g. metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium

or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example N-ethyl-piperidine or N,N'-dimethylpiperazine.

5

When a basic group and an acid group are present in the same molecule, a compound of formula I (or an N-oxide thereof) may also form internal salts.

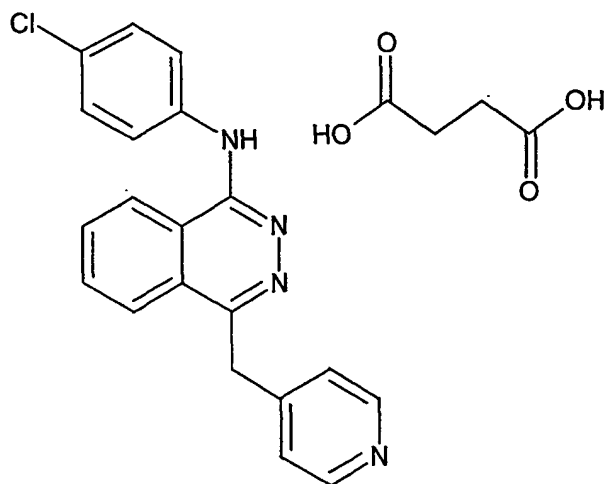
For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

15 In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

25

30

A preferred salt of the compounds a) is a succinate or hydrochloride. Such a succinate or hydrochloride is for example 1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride or (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]-ammonium hydrogen succinate (ZK).



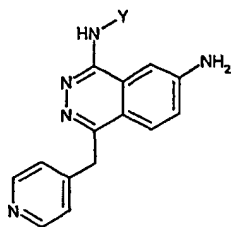
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Examples of compounds according to general formula I-A and I-AA (compound A) of the instant inventive combination are as in the following table:

Example	Name	Melting Point or MS
A-1	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine dihydrochloride	>270 °C
A-2	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	>270 °C
A-3	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	>270 °C
A-4	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine	194 -195 °C
A-5	1-(3-Chloroanilino)-4-(4-pyridylmethyl)phthalazine 1, 8 hydrochloride	233 - 236 °C
A-6	1-Anilino-4-(4-pyridylmethyl)-phthalazine dihydrochloride	217 - 220 °C
A-7	1-Benzylamino-4-(4-pyridylmethyl)phthalazine	137 - 138 °C
A-8	1-(4-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine	223 – 224 °C
A-9	1-(3-Benzyloxyanilino)-4-(4-pyridylmethyl)phthalazine	142 – 143 °C
A-10	1-(3-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine	118 – 120 °C
A-11	1-(4-Acetaminoanilino)- 4-(4-pyridylmethyl)phthalazine	>270 °C

Example	Name	Melting Point or MS
A-12	(S)-1-(1-Phenylethylamino)-4-(4-pyridylmethyl)phthalazine 1.85 hydrochlorid	190 °C
A-13	(R)-1-(1-Phenylethylamino)-4-(4-pyridylmethyl)phthalazine 1.85 dihydrochloride	190 °C
A-14	1-(2-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine	190 – 191 °C
A-15	1-(3-Pyridylamino)-4-(4-pyridylmethyl)phthalazine	137 – 139 °C
A-16	1-(4-Trifluoromethylanilino)-4-(4-pyridylmethyl)phthalazine	205 – 206 °C
A-17	1-(4-Fluoroanilino)-4-(4-pyridylmethyl)phthalazine	129 – 131 °C
A-18	1-(3-Hydroxyanilino)-4-(4-pyridylmethyl)phthalazine	217 – 219 °C
A-19	1-(4-Hydroxyanilino)-4-(4-pyridylmethyl)phthalazine	239 – 241 °C
A-20	1-(3-Aminoanilino)-4-(4-pyridylmethyl)phthalazine trimesylate	249 – 251 °C
A-21	1-(3,4-Dichloroanilino)-4-(4-pyridylmethyl)phthalazine	249 – 250 °C
A-22	1-(4-Bromoanilino)-4-(4-pyridylmethyl)phthalazine	201 – 202 °C
A-23	1-(3-Chloro-4-methoxyanilino)-4-(4-pyridylmethyl)phthalazine	195 – 197 °C
A-24	1-(4-Cyanoanilino)-4-(4-pyridylmethyl)phthalazine	228 – 230 °C

Example	Name	Melting Point or MS
A-25	7-Acetamino-1-(4-chloro-anilino)-4-(4-pyridylmethyl)-phthalazine hydrochloride	260 – 265 °C
A-26	7-Acetamino-1-(4-methoxyanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	160 – 163 °C
A-27	7-Acetamino-1-(3-methoxyanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	156 – 159 °C
A-28	7-Acetamino-1-(3-chloro-anilino)-4-(4-pyridylmethyl)-phthalazine hydrochloride	(M+H) 370
A-29	7-Acetamino-1-anilino-4-(4-pyridylmethyl)phthalazine hydrochloride	162 – 166 °C
A-30	7-Acetamino-1-(3,4-dichloro-anilino)-4-(4-pyridylmethyl)-phthalazine hydrochloride	
A-31	7-(Benzoyloxycarbonylamino)-1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	
A-32	7-Amino-1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	>300 °C



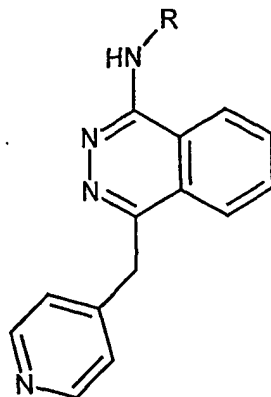
Example	-HN-Y	HPLC:t _{RET}	FAB MS (M+H) ⁺
A-33		10.5	362
A-34		9.0	328
A-35		10.3	342
A-36		9.5	358
A-37		9.7	358

Example	Name	Melting Point or MS
A-38	7-(3-Nitrobenzoylamino)-1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	
A-39	7-(3-Aminobenzoylamino)-1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	
A-40	7-(2-Hydroxyethylamino)-1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	
A-41	7-Bromo-1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride	
A-42	1-(4-Methylanilino)-4-(4-pyridylmethyl)phthalazine	152 – 153 °C
A-43	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine	207 – 209 °C
A-44	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine hemifumarate	202 °C
A-45	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine dimesylate	145 – 150 °C
A-46	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine dihydrochloride	268 – 270 °C

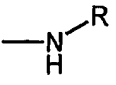
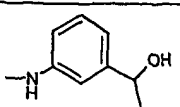
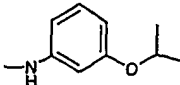
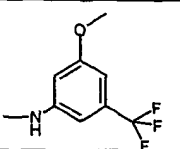
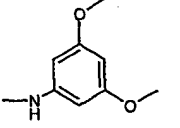
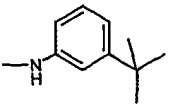
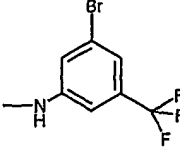
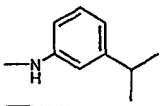
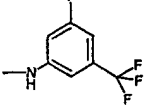
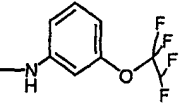
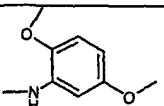
Example	Name	Melting Point or MS
A-47	1-(3-Chloro-4-fluoroanilino)-4-(4-pyridylmethyl)phthalazine	185 – 187 °C
A-48	1-(3-Methylanilino)-4-(4-pyridylmethyl)phthalazine	141 – 143 °C
A-49	1-(4-Ethylanilino)-4-(4-pyridylmethyl)phthalazine	163 – 164 °C
A-50	1-(4-Propylanilino)-4-(4-pyridylmethyl)phthalazine	180 – 181 °C
A-51	1-(3-Fluoro-4-methylanilino)-4-(4-pyridylmethyl)phthalazine	210 – 212 °C
A-52	1-(4-Chloro-2-fluoroanilino)-4-(4-pyridylmethyl)phthalazine	157 – 159 °C
A-53	1-(4-Ethoxyanilino)-4-(4-pyridylmethyl)phthalazine	223 – 224 °C
A-54	1-(4-Chloroanilino)-4-[(2-methyl-4-pyridyl)methyl]-phthalazine	158 – 159 °C
A-55	1-(4-Chloroanilino)-4-[(2,6-methyl-4-pyridyl)methyl]-phthalazine	175 – 176 °C
A-56	1-(4-Chloroanilino)-4-(4-pyridylmethyl)-5,6,7,8-tetrahydrophthalazine	181 – 183 °C
A-57	1-(3,4-Dimethylanilino)-4-(4-pyridylmethyl)phthalazine	180 – 181 °C
A-58	1-(3,5-Dimethylanilino)-4-(4-pyridylmethyl)phthalazine	174 – 175 °C

Example	Name	Melting Point or MS
A-59	1-(4-Isopropylanilino)-4-(4-pyridylmethyl)phthalazine dihydrochloride	>250 °C
A-60	1-(4-tert-Butylanilino)-4-(4-pyridylmethyl)phthalazine dihydrochloride	196 – 200 °C
A-61	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine	233 – 236 °C
A-62	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine	139 – 141 °C
A-63	1-(4-Chloroanilino)-4-(4-pyridylmethyl)-5,6,7,8-tetrahydrophthalazine	181 – 183 °C
A-64	1-(4-Ethoxyanilino)-4-(4-pyridylmethyl)phthalazine	223 – 224 °C
A-65	1-(4-Phenylanilino)-4-(4-pyridylmethyl)phthalazine	189 – 191 °C
A-66	1-(3,4,5-Trimethoxyanilino)-4-(4-pyridylmethyl)phthalazine	110 – 111 °C
A-67	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine-3-oxide	226 – 228 °C
A-68	1-(3-Hydroxyphenoxy)-4-(4-pyridylmethyl)phthalazine	206 – 207 °C
A-69	1-Cyclohexylamino-4-(4-pyridylmethyl)phthalazine	137 – 139 °C
A-70	1-Cyclopentylamino-4-(4-pyridylmethyl)phthalazine	163 – 165 °C
A-71	1-(4-Chloroanilino)-4-[(2-methyl-4-pyridyl)phthalazine	158 – 159 °C

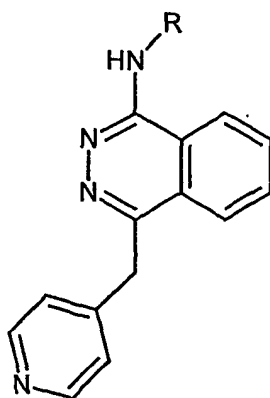
Example	Name	Melting Point or MS
A-72	1-(4-Chloroanilino)-4-[(2,6-dimethyl-4-pyridyl)methyl]-phthalazine	175 –176 °C
A-73	1-Cyclopropylamino-4-(4-pyridylmethyl)phthalazine. 1,58 hydrochloride	>250 °C
A-74	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate	
A-75	1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine oxalate	
A-76	<i>rac</i> 1-(4-Chloroanilino)-4-[1-(4-pyridyl)ethyl]phthalazine	132 –134 °C
A-77	1-(4-Chloroanilino)-4-[(1-oxypyridin-4-yl)methyl]-phthalazine	249 –251 °C
A-78	1-(4-Chloroanilino)-4-(4-pyrimidinylmethyl)phthalazine	174 –176 °C
A-79	1-(3-Phenoxyanilino)-4-(4-pyridylmethyl)phthalazine	186 –189 °C


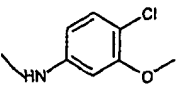
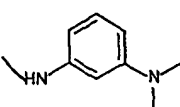
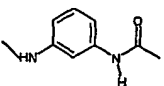
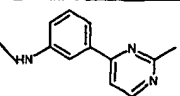
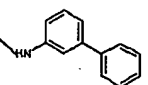
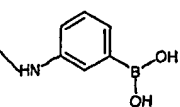


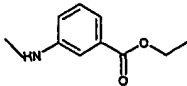
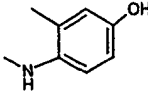
Example		m.p. [°C]
A-80		192-195
A-81		256-258
A-82		148-149
A-83		143-144
A-84		193-194
A-85		184-185
A-86		176-178
A-87		391/393
A-88		192-193

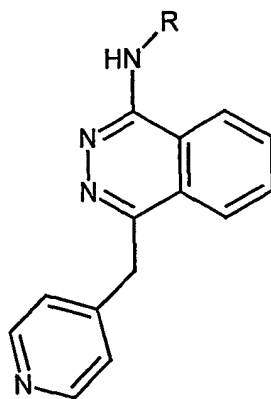
Example		m.p. [°C] or MS
A-89		221-222
A-90		188-190
A-91		143-145
A-92		193-196
A-93		MS: 369
A-94		223-226
A-95		MS 355
A-96		253-255
A-97		185-187
A-98		199-201

Example	Name	Melting Point
A-99	1-(3-Decyloxyanilino)-4-(4-pyridylmethyl)phthalazine	116 – 119 °C


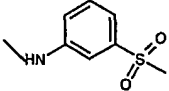
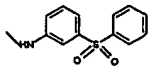
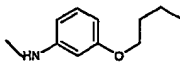
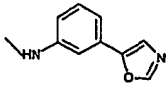



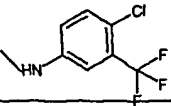
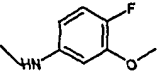
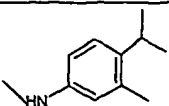
Example		m.p. [°C]
A-100		242-243
A-101		143-145
A-102		263-265
A-103		214-216
A-104		MS 389
A-105		MS 357

Example		m.p. [°C]
A-106		153-155
A-107		MS 343



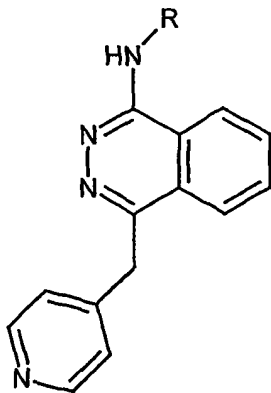
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
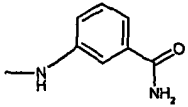
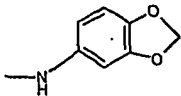
Example		m.p. [°C]
A-108		239-241
A-109		196-199
A-110		MS 399
A-111		194-196

Example		m.p. [°C]
A-112		220-222
A-113		190-192
A-114		163-166

Example	Name	Melting Point
A-115	1-[(4-Acetyl-3-hydroxyanilino)-4-(4-pyridylmethyl)phthalazine	234 – 236 °C

5

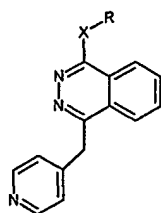


Example		m.p. [°C]
A-116		266-268
A-117		186-188

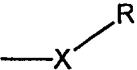
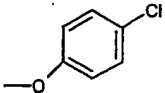
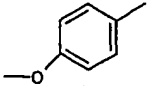
Example	Name	Melting Point or MS
A-118	1-(3-Acetylanilino)-4-(4-pyridylmethyl)phthslazine	229 – 231 °C
A-119	1-[(2'-Methyl-1',3'-dioxolan-2'-yl)anilino-4-(4-pyridylmethyl)phthalazine	(M+H)+ 399
A-120	1-(4-Chloro-3-hydroxyanilino)-4-(4-pyridylmethyl)phthalazine	245 – 246 °C
A-121	1-(3-Chlorophenoxy)-4-(4pyridylmethyl)phthalazine	143 – 145 °C

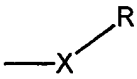
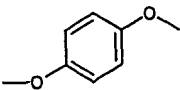
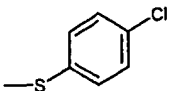
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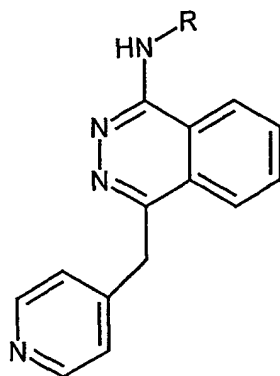
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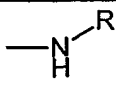
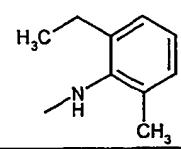
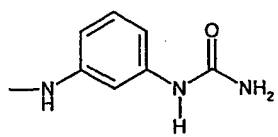
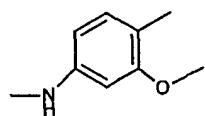
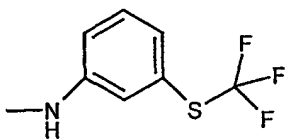
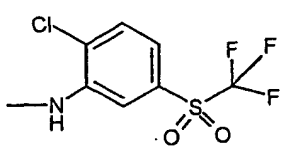
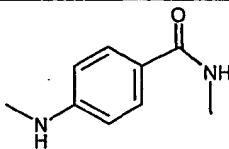
Example		m.p. [°C]
A-122		207-208
A-123		175-176

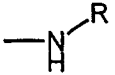
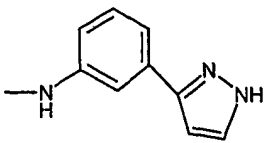
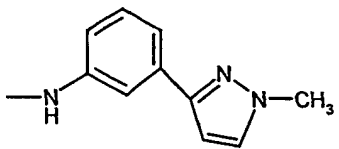
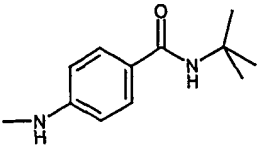
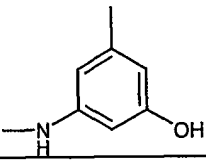
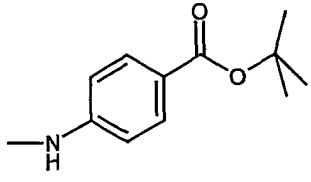
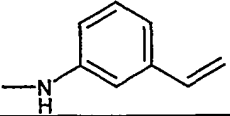
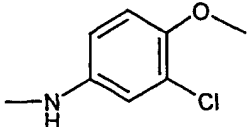
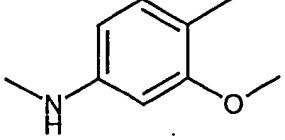
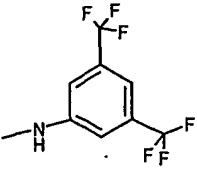
Example		m.p. [°C]
A-124		194-196
A-125		204-206

5

Example	Name	Melting point or MS
A-126	5-(4-Chloroanilino)-8-(4-pyridylmethyl)pyrido[2.3]-dipyridazine	220 – 222 °C
A-127	8-(4-Chloroanilino)-5-(4-pyridylmethyl)pyrido[2.3-d]pyridazine	196 – 197 °C
A-128	1-(4-Chloroanilino)-4-(4-pyridylmethyl)pyrido[3.4-d]]pyridazine	227 – 228 °C
A-129	4-(1-Chloroanilino)-4-(4-pyridylmethyl)pyrido[3.4-d]]pyridazine	220 – 221 °C
A-130	racBenzoic acid-[4-(4-chloroanilino)phthalazin-1-yl]-(pyridin-4-yl)methyl ester	183 – 185 °C
A-131	rac[4-(4-chloroanilino)-phthalazin-1-yl](pyridin-4-yl)methanol	MS 363



Example		Melting Point or MS
A-132		
A-133		
A-134		
A-135		
A-136		
A-137		

Example		Melting Point or MS
A-138		
A-139		
A-140		
A-141		
A-142		
A-143		
A-144		
A-145		
A-146		

Example	Name	Melting point or MS
A-147	3-(4-Chloroanilino)-4.5-dimethyl-6-(pyridin-4-yl)methylpyridazine	196 – 199 °C
A-148	3-(4-Methylanilino)-4.5-dimethyl-6-(pyridin-4-yl)methylpyridazine	86 – 70 °C
A-149	3-(4-Methoxyanilino)-4.5-dimethyl-6-(pyridin-4-yl)methylpyridazine	MS 321
A-150	3-(3-Chloroanilino)-4.5-dimethyl-6-(pyridin-4-yl)methylpyridazine	164 – 167 °C
A-151	3-(3-Methylanilino)-4.5-dimethyl-6-(pyridin-4-yl)methylpyridazine	68 – 90 °C

5

It should however be noted that these examples do not limit the inventive combination only to these compounds A.

The process for the production of the above mentioned compounds is completely described in WO 98/35958.

10

On the other hand, histone modification, catalized by the histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes, plays an important role in regulating gene expression by altering chromatin structure.

5 Histone acetylation results in charge neutralization and separation of DNA from the histones. Thus, transcriptionally activated genes are typically associated with hyperacetylated loci. Because of the profound effect of histone modification on gene transcription, manipulation of the activities of histone-modifying HAT and HDAC enzymes has the potential for modifying the cell cycle
10 and the neoplastic transformation of cells. Some compounds with deacetylase inhibitory activity have been shown to be effective in suppressing tumor growth in animal models and in initial clinical trials, although the efficacy is limited, possibly due to their stability, low retention, or nonspecific toxicity in the body.

15 In addition, HDAC enzymes play a role in the regulation of hypoxia-induced angiogenesis. Hypoxia enhances HDAC function and HDAC is closely involved in angiogenesis through suppression of hypoxia-responsive tumor suppressor genes. A specific HDAC inhibitor upregulates p53 and von Hippel-Lindau expression and downregulates hypoxia-induced factor-1alpha and vascular
20 endothelial growth factor (VEGF). HDAC inhibitors are also shown to inhibit angiogenesis both in vitro and in vivo.

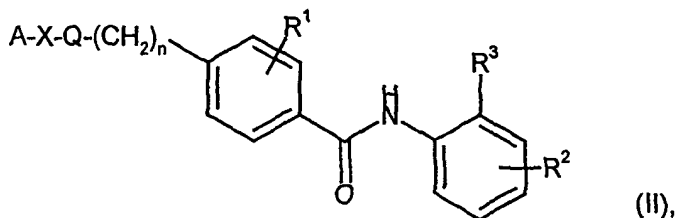
HDAC inhibitors are currently of major interest as potential anti-cancer therapeutics, largely because of their well-documented properties of inhibiting
25 proliferation and induce apoptosis of tumour cells. Furthermore, the finding that HDAC appears to be a critical regulator of angiogenesis in addition to tumour cell growth will cause further interest in the development of HDAC inhibitors as potential anticancer drugs.

30 In EP 0847992 (US 6,174,905) benzamide derivatives are described which show differentiation-inducing effects, and which are useful a therapeutic or improving agent for malignant tumors, autoimmune diseases, dermatologic

diseases and parasitism. In particular, they are highly effective as an anticancer drug, specifically to a hematologic malignancy and a solid carcinoma.

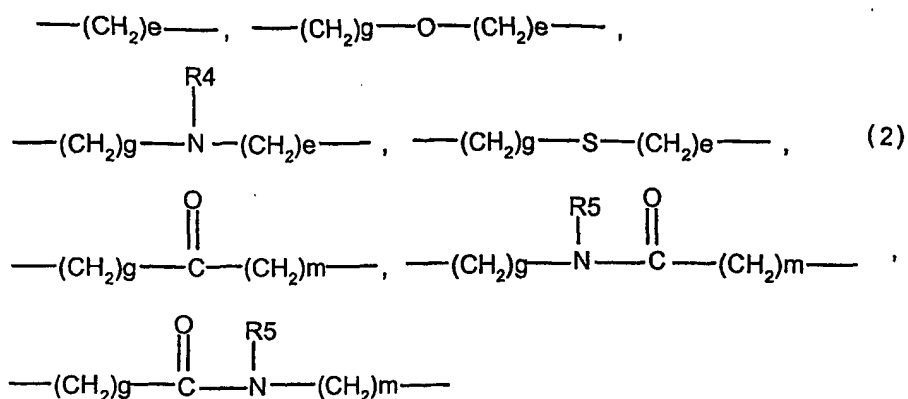
These compounds of general formula II

5



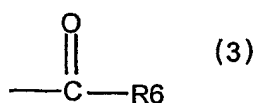
wherein

- A is an optionally substituted phenyl group or an optionally substituted heterocyclic group wherein the substituent(s) for the phenyl group or the heterocyclic group is (are) 1 to 4 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;
- X is a bond or a moiety having the following structure



wherein e is an integer of 1 to 4; g and m are independently an integer of 0 to 4;

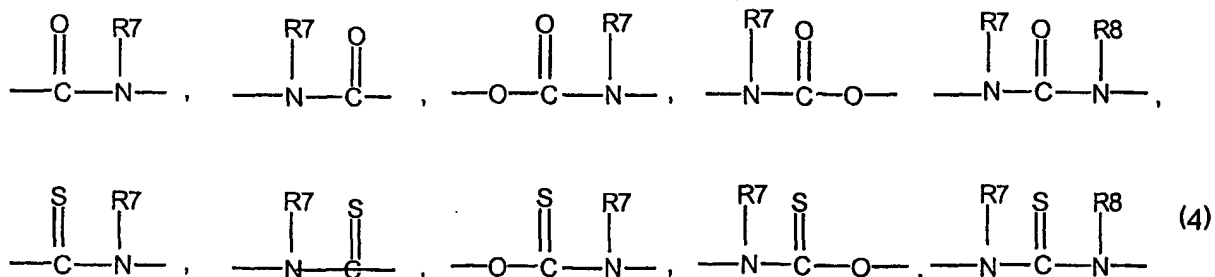
- 10 R^4 is a hydrogen atom or an optionally substituted alkyl group having 1 to 4 carbons, or the acyl group represented by formula (3)



wherein R^6 is an optionally substituted alkyl group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a phenyl group or a heterocyclic group; R^5 is a hydrogen atom or an optionally substituted alkyl group having 1 to 4 carbons;

- 20 n is an integer of 0 to 4, provided that when X is a bond, n is not zero;

Q is a moiety having a structure selected from those illustrated in formula (4)



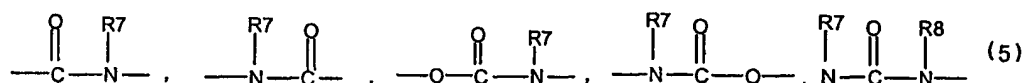
wherein R^7 and R^8 are independently a hydrogen atom or an optionally substituted alkyl group having 1 to 4 carbons;

R^1 and R^2 are independently a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkoxy group having 1 to 4 carbons, a carboxyl group or an alkoxycarbonyl group having 1 to 4 carbons;

10 R^3 is a hydroxyl or amino group or a pharmaceutically acceptable salt thereof.

Of special interest are those compounds of formula II), wherein n is an integer of 1 to 4.

15 Of further interest are those compounds wherein Q is selected from the structures illustrated in formula (5):



20

wherein R7 and R8 are as defined above.

Of further interest are also those compounds wherein A is an optionally substituted hetero ring, especially an optionally substituted pyridyl group.

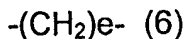
25

Of special interest are also those compounds of general formula II), wherein n is 1 to 4; Q is selected from the structures illustrated in formula (5); A is an optionally substituted hetero ring, especially optionally substituted pyridyl group; most preferred, wherein X is direct bond, most preferred wherein R^1 and R^2 are a hydrogen atom, most preferred, wherein R^3 is an amino group.

30

Of special interest are also those compounds of general formula II), wherein n is

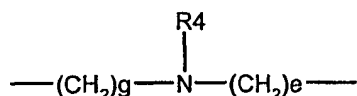
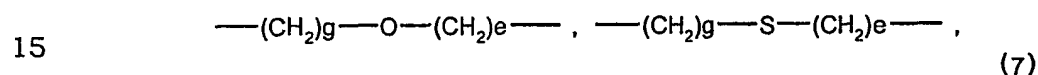
1 to 4; wherein Q is selected from the structures illustrated in formula (5); A is an optionally substituted hetero ring, especially optionally substituted pyridyl group; most preferred, wherein X is the structure represented by formula (6):



- 5 wherein e is an integer of 1 to 4; most preferred wherein n is 1 and R¹ and R² are a hydrogen atom; most preferred, wherein R³ is an amino group.

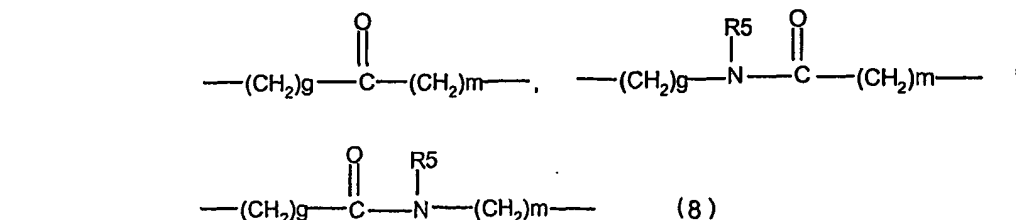
Of special interest are also those compounds of general formula II), wherein Q is selected from the structures illustrated in formula (5); A is an optionally substituted hetero ring, especially optionally substituted pyridyl group; most preferred, wherein X is selected from the structures illustrated in formula (7):

wherein e, g and R⁴ are as defined above; most preferred wherein n is 1 and R¹



- 20 and R² are a hydrogen atom; most preferred, wherein R³ is an amino group.

Of special interest are also those compounds of general formula II), wherein Q is selected from the structures illustrated in formula (5); A is an optionally substituted hetero ring, especially optionally substituted pyridyl group; most preferred, wherein X is selected from the structures illustrated in formula (8):

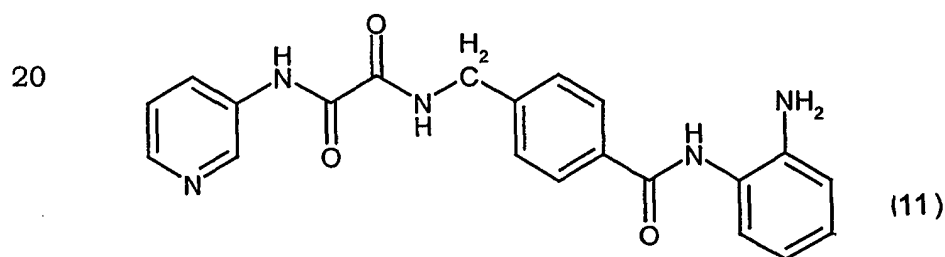
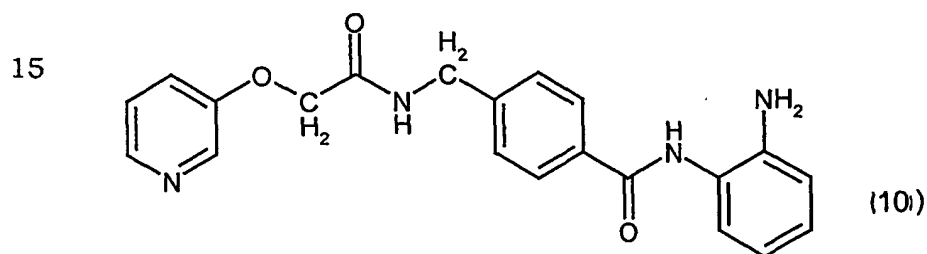
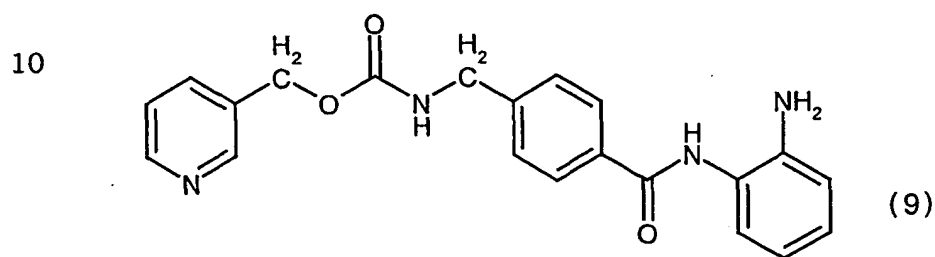


- 30 wherein g, m and R⁵ are as defined above; most preferred wherein n is 1 and R¹ and R² are a hydrogen atom; most preferred, wherein R³ is an amino group.

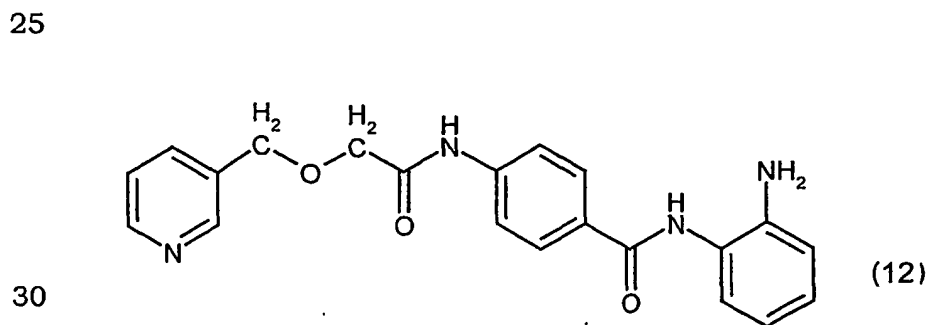
Of special interest are also those compounds of general formula II), wherein n is

zero, and further of interest, wherein Q is selected from the structures illustrated in formula (5), and further of interest, wherein A is an optionally substituted hetero ring, most preferred, wherein A is an optionally substituted pyridyl group, most preferred, wherein R¹ and R² are a hydrogen atom, most preferred, wherein R³ is an amino group.

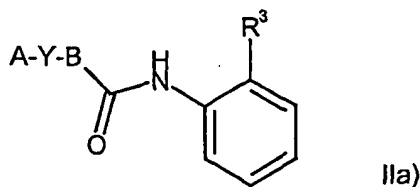
Selected compounds of general formula II are for example the following compounds:



and



The inventive combination may also comprise a compound of general Formula IIa)



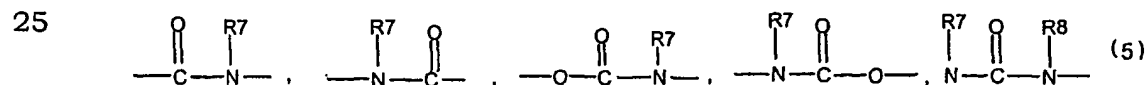
- 5 wherein A and R³ are as defined above; B is an optionally substituted phenyl or heterocycle group; Y is a moiety having --CO--, --CS--, --SO-- or --SO₂-- which is linear, cyclic or their combination and links A and B; and in which the distances between the centroid of ring B (W1), the centroid of ring A (W2) and an oxygen or sulfur atom as a hydrogen bond acceptor in the moiety Y (W3) can
 10 be as follows; W1-W2=6.0 to 11.0 Å, W1-W3=3.0 to 8.0 Å, and W2-W3=3.0 to 8.0 Å; preferably W1-W2=7.0 to 9.5 Å; W1-W3 is 3.0 to 5.0 Å; and W2-W3 is 5.0-8.0 Å; or a pharmaceutically acceptable salt thereof.

Interesting compounds are those compounds of formula IIa), wherein A is an
 15 optionally substituted heterocycle; R³ is an amino group; and Y is a moiety having --CO-- which is linear, cyclic or their combination and links A and B.

Of further interest are those compounds of general Formula IIa), wherein B is an optionally substituted phenyl; W1-W2 is 7.0 to 9.5 Å; W1-W3 is 3.0 to 5.0 Å;
 20 and W2-W3 is 5.0 to 8.0 Å.

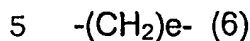
In the above formula (II), n maybe zero or an integer of 1 to 4.

Q in the above formula (II) may be any structure illustrated in formula (5);



wherein R7 and R8 are as defined above.

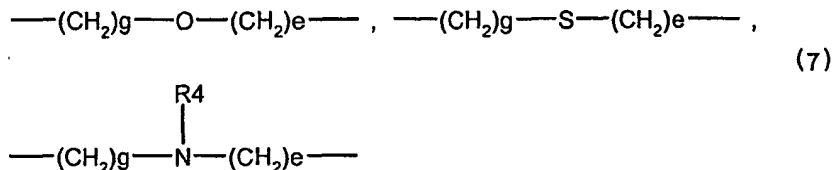
X in the above formula (II) may be a moiety having the structure represented by formula (6);



wherein e is as defined above.

X in the above formula (II) may be also a moiety having any structure illustrated in formula (7);

10

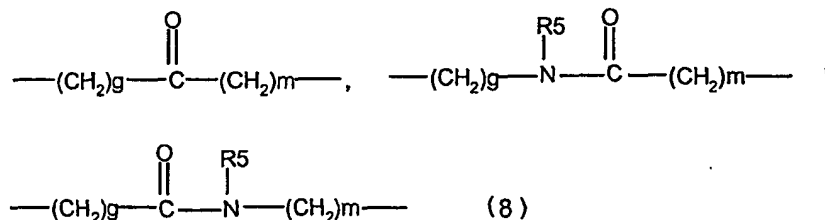


15

wherein e, g and R⁴ are as defined above.

X in the above formula (II) may be also a moiety having any structure illustrated in formula (8);

20



25

wherein g, m and R⁵ are as defined above.

The compounds represented by formula (IIa) may be one wherein A is an optionally substituted heterocycle; B is an optionally substituted phenyl; and R³ is an amino group.

30

These compounds may be also one wherein Y has --CO-- and is linear, cyclic or their combination.

5

As used herein, "1 to 4 carbons" means a carbon number per a single substituent; for example, for dialkyl substitution it means 2 to 8 carbons.

A heterocycle in the compound represented by formula (II) or (IIa) is a
10 monocyclic heterocycle having 5 or 6 members containing 1 to 4 nitrogen, oxygen or sulfur atoms or a bicyclic-fused heterocycle. The monocyclic heterocycle includes pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, pyrrole, pyrazole, isoxazole, isothiazole, imidazole, oxazole, thiazole, piperidine, piperazine, pyrrolidine, quinuclidine, tetrahydrofuran, morpholine,
15 thiomorpholine and the like. The bicyclic fused heterocycle includes quinoline; isoquinoline; naphthyridine; fused pyridines such as furopyridine, thienopyridine, pyrrolopyridine, oxazolopyridine, imidazolopyridine and thiazolopyridine; benzofuran; benzothiophene; benzimidazole and the like.

20 A halogen may be fluorine, chlorine, bromine or iodine.

An alkyl having 1 to 4 carbons includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

25 An alkoxy having 1 to 4 carbons includes methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

An aminoalkyl having 1 to 4 carbons includes aminomethyl, 1-aminoethyl, 2-aminopropyl and the like.

30

An alkylamino having 1 to 4 carbons includes N-methylamino, N,N-dimethylamino, N,N-diethylamino, N-methyl-N-ethylamino, N,N-

diisopropylamino and the like.

An acyl having 1 to 4 carbons includes acetyl, propanoyl, butanoyl and like.

- 5 An acylamino having 1 to 4 carbons includes acetylamino, propanoylamino, butanoylamino and the like.

An alkylthio having 1 to 4 carbons includes methylthio, ethylthio, propylthio and the like.

10

A perfluoroalkyl having 1 to 4 carbons includes trifluoromethyl, pentafluoroethyl and the like.

- 15 A perfluoroalkyloxy having 1 to 4 carbons includes trifluoromethoxy, pentafluoroethoxy and the like.

An alkoxycarbonyl having 1 to 4 carbons includes methoxycarbonyl and ethoxycarbonyl.

- 20 An optionally substituted alkyl having 1 to 4 carbons includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl and these having 1 to 4 substituents selected from the group consisting of a halogen, hydroxyl, amino, nitro, cyano, phenyl and a heterocycle.

- 25 As described below, important elements in the compound represented by formula (IIa) are (a) presence of ring A, ring B and oxygen or sulfur atom as a hydrogen bond acceptor, and (b) the distances between them determined by their steric configurations. There may be, therefore, no limitation as long as the structure of Y has a hydrogen bond acceptor and rings A and B have required
30 steric configurations. Specifically, the structure of Y which has --CO--, --CS--, --SO-- or --SO₂-- and links A and B and which is linear, cyclic or their combination, means either (a) one consisting of carbon and/or hetero atoms

linking A and B, whose linear or branched moiety has --CO--, --CS--, --SO-- or --SO₂--; (b) one linking A and B, whose cyclic moiety has --CO--, --CS--, --SO-- or --SO₂--; and (c) one linking A and B wherein a combination of cyclic and linear moieties form a structural unit having --CO--, --CS--, --SO-- or --SO₂--.

5

A basic cyclic structure includes cyclic moieties having 4 to 7 members containing carbons and/or hetero atoms or their fused cycles. For example it may be cyclobutane, cyclopentane, cyclohexane, cycloheptane, oxetane, oxolane, oxane, oxepane, pyrrolidine, imidazolidine, pyrazolidine, piperidine, 10 piperazine, indoline, isoindoline, thiolane, thiazolidine and oxazolidine rings, which may contain unsaturated bonds, hydrogen bond acceptors and/or substituents.

Structural analyses considering degree of conformational freedom of the 15 compound represented by formula (IIa) have indicated that atomic groups possibly involved in an biomolecule-drug interaction such as a hydrophobic interaction and hydrogen bond may have a particular spatial configuration in a compound showing high differentiation-inducing effect.

20 In the above analyses, other commercially available program packages such as CATALYST(MSI), Cerius 2/QSAR+(MSI) and SYBYL/DISCO(Tripos) may be used, and the information on distance obtained here is not limited to that from a particular calculation program.

25

The ring centroid used in definition of the spatial configuration may be defined as an average of X, Y and Z axes of the ring-forming atoms. When a ring structure to be calculated is fused-polycyclic, the centroid of either the overall fused ring or of a partial ring may be used as that for defining the space.

30

"Possibility of formation of a configuration" means that a conformer filling the spatial configuration is within 15 kcal/mol, preferably 8 kcal/mol from the

energetically most stable structure.

Specific calculation can be performed as described in the instructions for Sybyl (M.Clark) or J.Comput.Chem. 10, 982(1989).

5

A pharmaceutically acceptable salt of the compound of this invention includes salts with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid; and with an organic acid such as acetic acid, lactic acid, tartaric acid, malic acid, succinic acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluoroacetic acid, p-toluenesulfonic acid and methanesulfonic acid. Such a salt includes N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide hydrochloride, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide hydrobromide, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide sulfate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide phosphate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide acetate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide lactate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide tartrate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide malate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide succinate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide fumarate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide maleate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide citrate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide trifluoroacetate, N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide p-toluenesulfonate and N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide methanesulfonate.

When having asymmetric carbon or carbons, the compound represented by formula (II) or (IIa) may be obtained as an individual stereoisomer or a mixture of stereoisomers including a racemic modification. This invention encompasses the above-specified different forms, which may be also used as an active
5 ingredient.

Representative compounds b) represented by formula (II) or (IIa) are specifically shown in Tables 1 to 4, but this invention is not intended to be limited to these.

Table 1

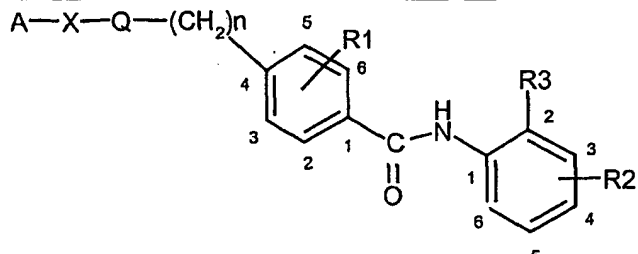
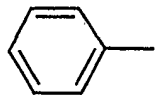
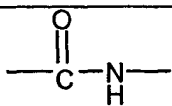
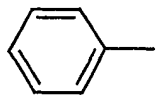
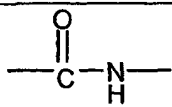
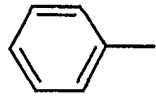
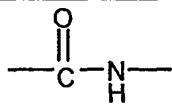
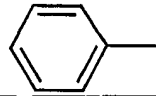
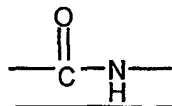
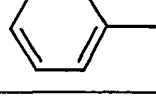
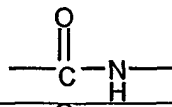
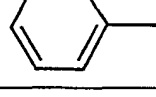
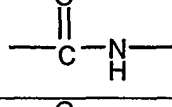
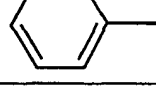
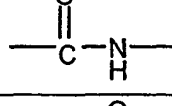
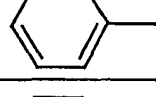
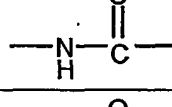
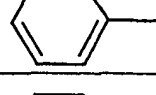
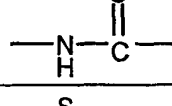
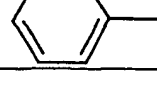
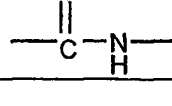
							
Compound No.	A	X	Q	n	R1	R2	R3
1		Direct bond		1	H	H	NH ₂
2		-CH ₂ -		0	H	H	NH ₂
3		-(CH ₂) ₂ -		0	H	H	NH ₂
4		-(CH ₂) ₃ -		0	H	H	NH ₂
5		-(CH ₂) ₄ -		0	H	H	NH ₂
6		-CH ₂ -		1	H	H	NH ₂
7		-(CH ₂) ₂ -		1	H	H	NH ₂
8		-CH ₂ -		0	H	H	NH ₂
9		-(CH ₂) ₂ -		0	H	H	NH ₂
10		Direct bond		1	H	H	NH ₂

Table 1

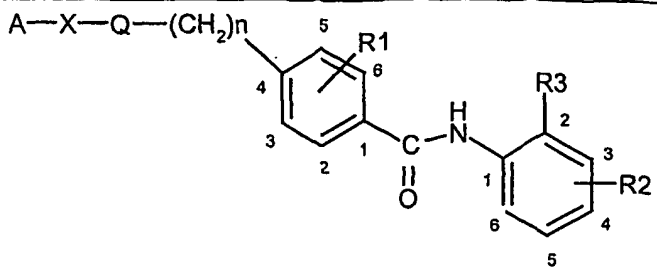
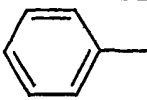
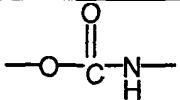
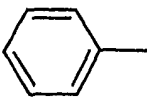
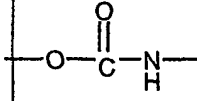

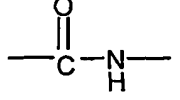
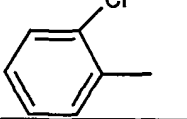
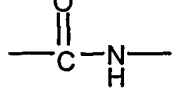
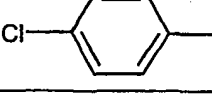
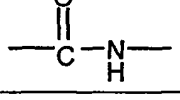
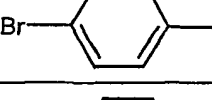
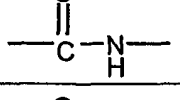
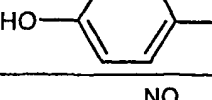
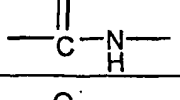
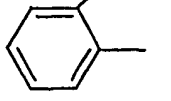
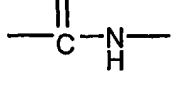
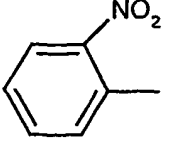
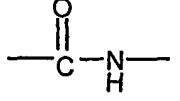
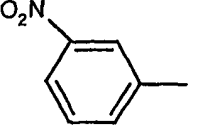
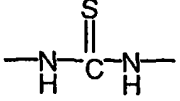
							
Compound No.	A	X	Q	n	R1	R2	R3
11		-CH ₂ -		1	H	H	NH ₂
12		Direct bond		1	H	H	NH ₂
13		Direct bond		1	H	H	NH ₂
14		Direct bond		1	H	H	NH ₂
15		-CH ₂ -		0	H	H	NH ₂
16		Direct bond		1	H	H	NH ₂
17		Direct bond		1	H	H	NH ₂
18		Direct bond		1	H	H	NH ₂
19		-CH ₂ -		0	H	H	NH ₂
20		Direct bond		1	H	H	NH ₂

Table 1

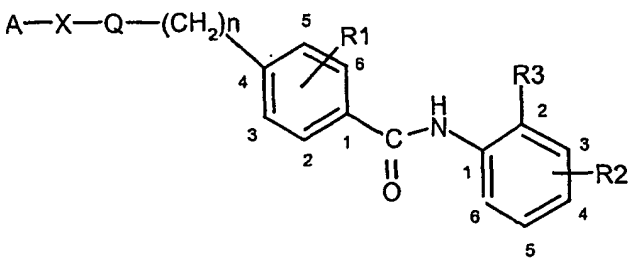
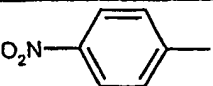
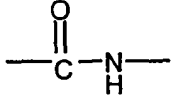
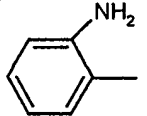
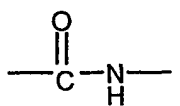
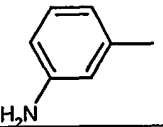
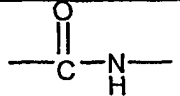
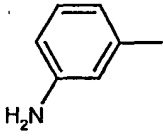
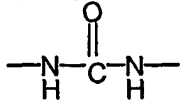
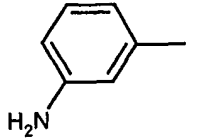
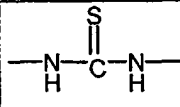
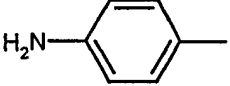
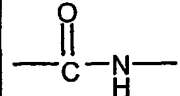
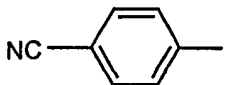
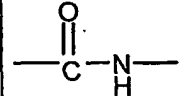
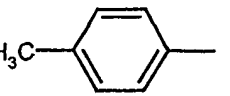
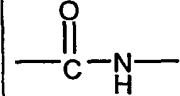
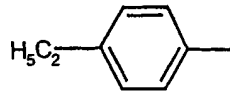
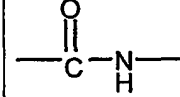
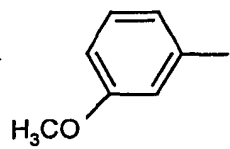
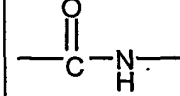
							
Compound No.	A	X	Q	n	R1	R2	R3
21		-CH ₂ -		0	H	H	NH ₂
22		-CH ₂ -		0	H	H	NH ₂
23		-CH ₂ -		1	H	H	NH ₂
24		Direct bond		1	H	H	NH ₂
25		Direct bond		1	H	H	NH ₂
26		-CH ₂ -		0	H	H	NH ₂
27		Direct bond		1	H	H	NH ₂
28		Direct bond		1	H	H	NH ₂
29		Direct bond		1	H	H	NH ₂
30		Direct bond		1	H	H	NH ₂

Table 1

$$A-X-Q-(CH_2)_n$$

Compound No.	A	X	Q	n	R1	R2	R3
31		Direct bond		1	H	H	NH ₂
32		-CH ₂ -		0	H	H	NH ₂
33		Direct bond		1	H	H	NH ₂
34		-CH ₂ -		1	H	H	NH ₂
35		Direct bond		1	H	H	NH ₂
36		Direct bond		1	H	H	NH ₂
37		Direct bond		1	H	H	NH ₂
38		-CH ₂ -		1	H	H	NH ₂
39		-CH ₂ -		1	H	H	NH ₂
40		Direct bond		1	H	H	NH ₂

Table 1

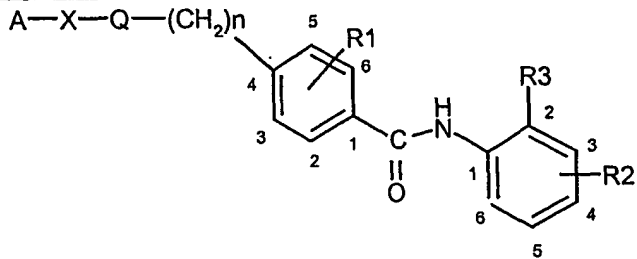
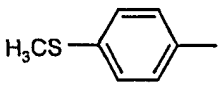
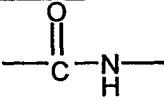
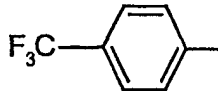
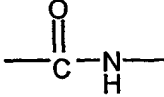
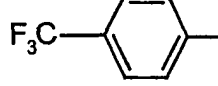
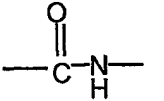
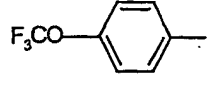
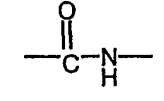
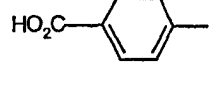
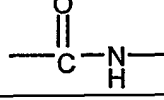
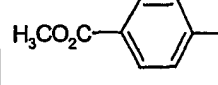
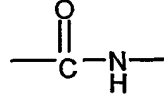
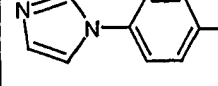
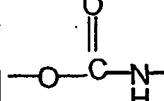
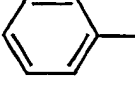
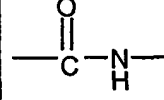
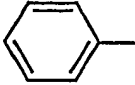
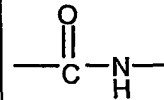
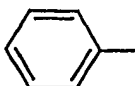
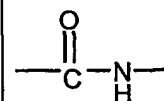
							
Compound No.	A	X	Q	n	R1	R2	R3
41		Direct bond		1	H	H	NH ₂
42		Direct bond		1	H	H	NH ₂
43		-CH ₂ -		0	H	H	NH ₂
44		Direct bond		1	H	H	NH ₂
45		Direct bond		1	H	H	NH ₂
46		Direct bond		1	H	H	NH ₂
47		-CH ₂ -		1	H	H	NH ₂
48		-O-CH ₂ -		1	H	H	NH ₂
49		-S-CH ₂ -		1	H	H	NH ₂
50		-NH-CH ₂ -		1	H	H	NH ₂

Table 1

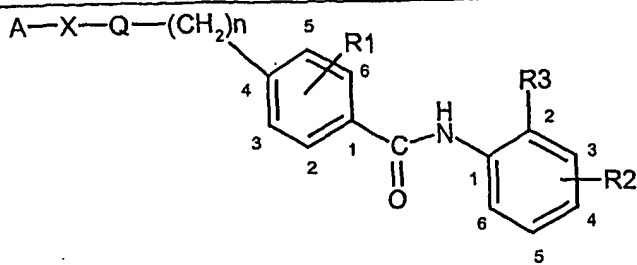
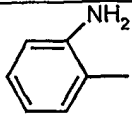
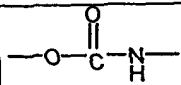
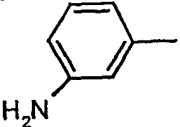
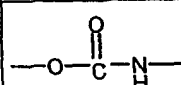
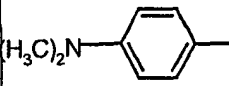
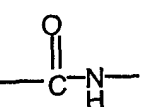
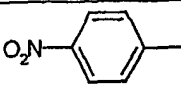
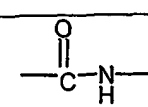
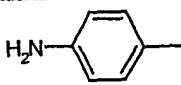
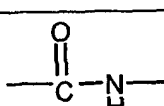
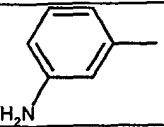
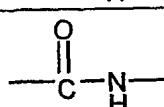
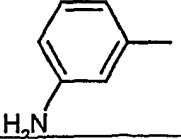
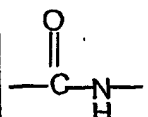
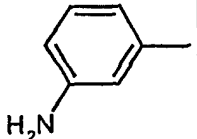
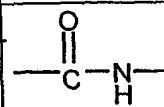
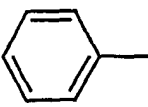
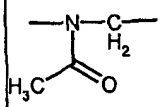
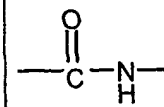
							
Compound No.	A	X	Q	n	R1	R2	R3
51		-CH ₂ -		1	H	H	NH ₂
52		-CH ₂ -		1	H	H	NH ₂
53		-CH ₂ -		0	H	H	NH ₂
54		-O-CH ₂ -		0	H	H	NH ₂
55		-O-CH ₂ -		0	H	H	NH ₂
56		-O-CH ₂ -		1	H	H	NH ₂
57		-O-CH ₂ -		1	H	H	NH ₂
58		-CH ₂ -O-CH ₂ -		0	H	H	NH ₂
59				1	H	H	NH ₂

Table 1

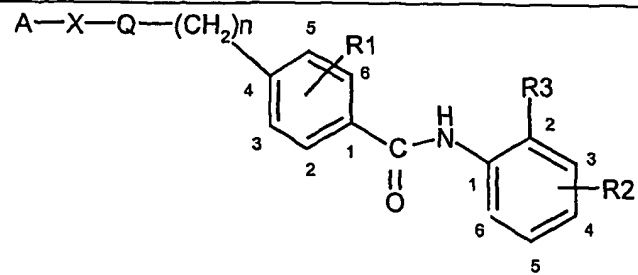
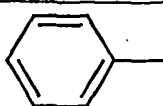
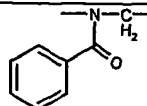
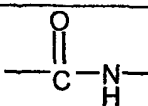
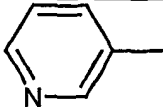
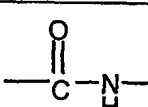
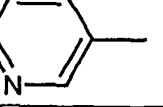
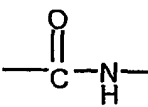
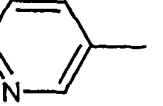
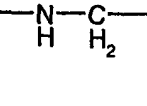
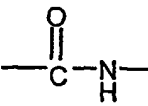
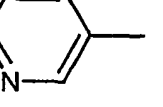
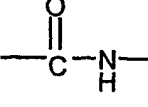
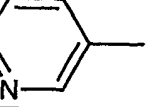
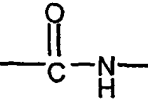
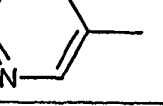
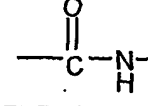
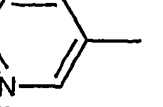
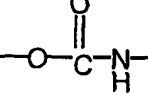
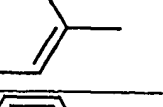
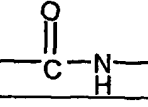
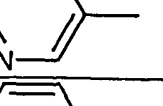
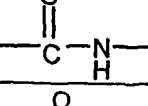
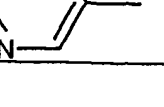
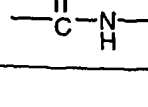
							
Compound No.	A	X	Q	n	R1	R2	R3
60				1	H	H	NH ₂
61		-O-CH ₂ -		1	H	H	NH ₂
62		-O-(CH ₂) ₂ -		1	H	H	NH ₂
63				1	H	H	NH ₂
64		-S-CH ₂ -		1	H	H	NH ₂
65		-O-CH ₂ -		0	H	H	NH ₂
66		-O-(CH ₂) ₂ -		0	H	H	NH ₂
67		-O-(CH ₂) ₂ -		0	H	H	NH ₂
68		-CH ₂ -		0	H	H	NH ₂
69		-(CH ₂) ₂ -		0	H	H	NH ₂
70		-(CH ₂) ₃ -		0	H	H	NH ₂

Table 1

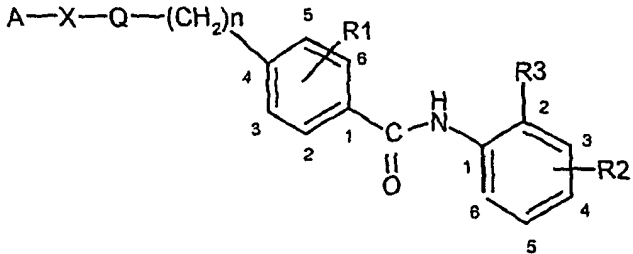
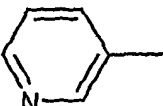
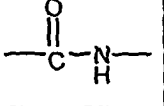
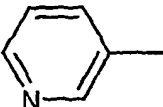
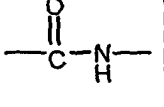
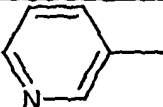
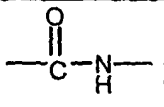
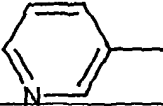
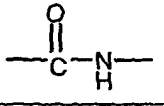
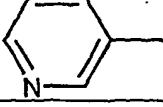
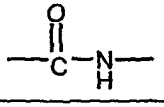
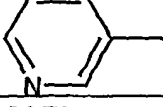
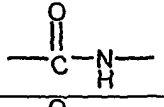
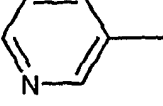
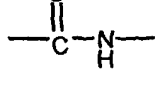
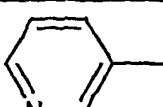
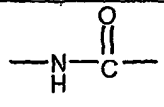
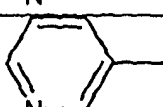
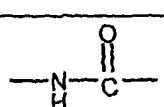
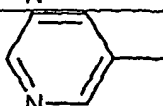
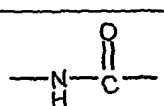
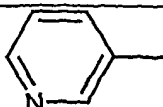
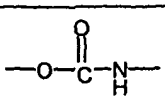
							
Compound No.	A	X	Q	n	R1	R2	R3
71		Direct bond		1	H	H	NH ₂
72		Direct bond		2	H	H	NH ₂
73		Direct bond		3	H	H	NH ₂
74		-CH ₂ -		1	H	H	NH ₂
75		-(CH ₂) ₂ -		1	H	H	NH ₂
76		-(CH ₂) ₃ -		1	H	H	NH ₂
77		-CH ₂ -		2	H	H	NH ₂
78		-CH ₂ -		1	H	H	NH ₂
79		Direct bond		2	H	H	NH ₂
80		-CH ₂ -		2	H	H	NH ₂
81		Direct bond		1	H	H	NH ₂

Table 1

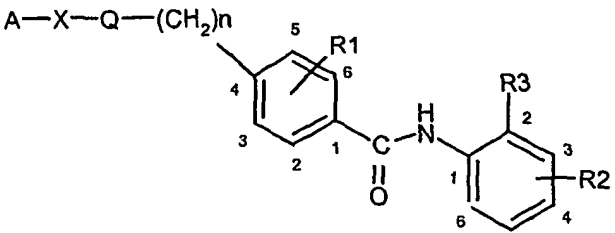
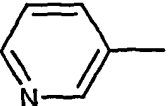
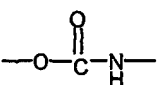
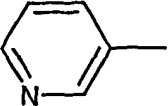
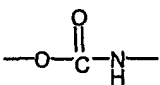
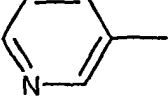
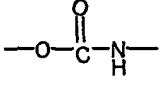
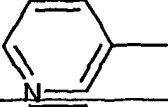
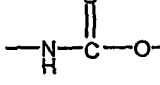
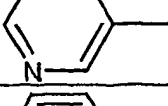
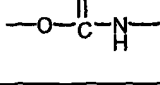
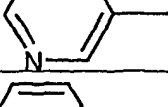
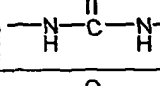
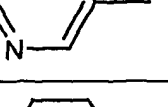
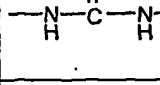
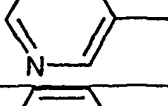
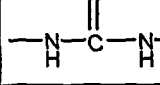
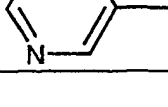
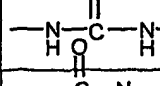
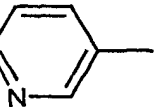
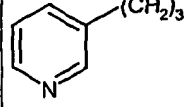
							
Compound No.	A	X	Q	n	R1	R2	R3
82		-CH ₂ -		1	H	H	NH ₂
83		-(CH ₂) ₂ -		1	H	H	NH ₂
84		-(CH ₂) ₃ -		1	H	H	NH ₂
85		-CH ₂ -		1	H	H	NH ₂
86		-CH ₂ -		1	H	H	NH ₂
87		Direct bond		1	H	H	NH ₂
88		-CH ₂ -		1	H	H	NH ₂
89		-(CH ₂) ₂ -		1	H	H	NH ₂
90		-CH ₂ -		1	H	H	NH ₂
91		-O-CH ₂ -		1	H	H	NH ₂

Table 1

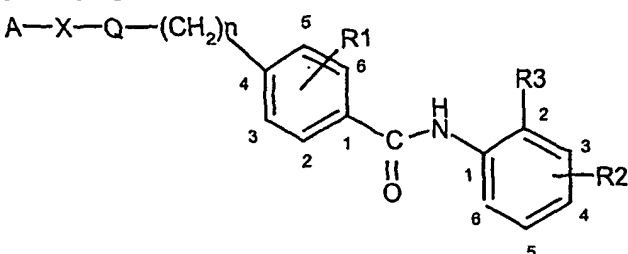
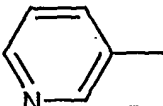
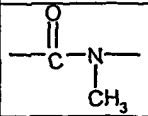
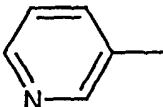
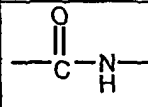
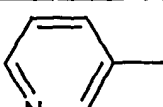
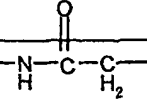
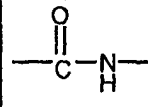
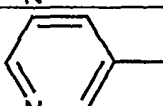
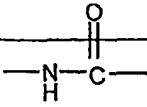
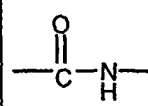
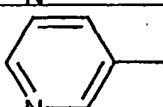
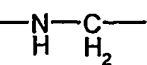
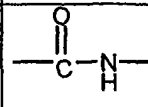
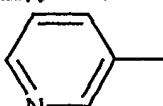
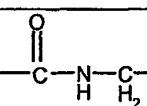
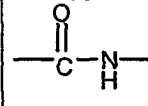
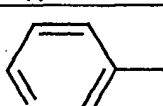
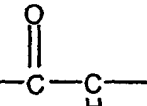
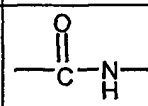
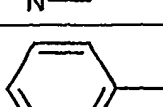
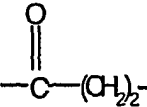
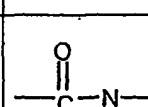
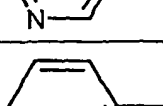
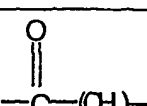
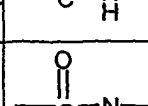
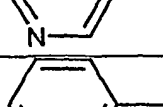
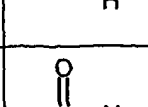
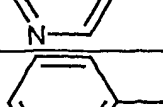
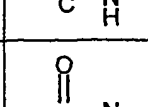
							
Compound No.	A	X	Q	n	R1	R2	R3
92		-O-CH ₂ -		1	H	H	NH ₂
93		-O-CH ₂ -		1	H	H	NH ₂
94				0	H	H	NH ₂
95				1	H	H	NH ₂
96				1	H	H	NH ₂
97				0	H	H	NH ₂
98				1	H	H	NH ₂
99				0	H	H	NH ₂
100				1	H	H	NH ₂
101		-CH ₂ -O-CH ₂ -		0	H	H	NH ₂
102		-CH ₂ -O-CH ₂ -		0	3-CH ₃	H	NH ₂

Table 1

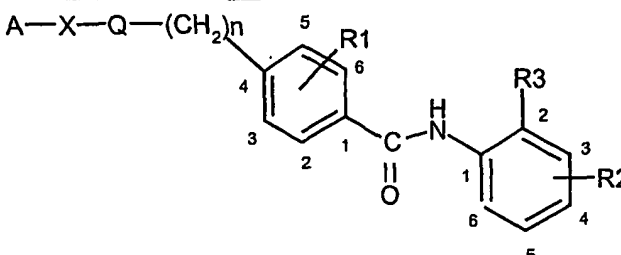
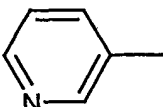
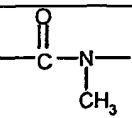
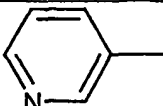
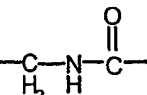
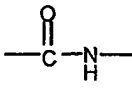
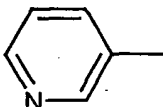
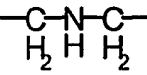
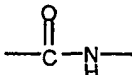
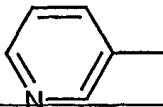
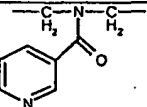
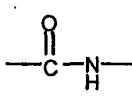
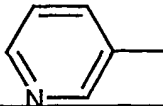
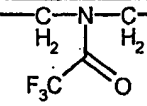
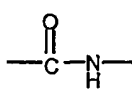
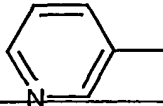
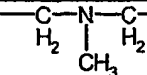
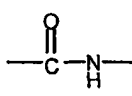
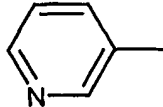
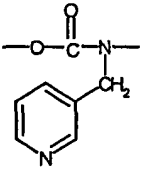
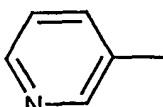
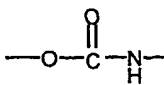
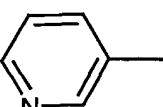
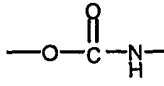
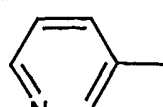
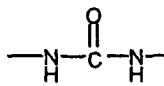
							
Compound No.	A	X	Q	n	R1	R2	R3
103		$-\text{CH}_2-\text{O}-\text{CH}_2-$		0	H	H	NH_2
104				0	H	H	NH_2
105				0	H	H	NH_2
106				0	H	H	NH_2
107				1	H	H	NH_2
108				0	H	H	NH_2
109		$-\text{CH}_2-$		1	H	H	NH_2
110		$-\text{CH}_2-$		1	H	5-F	NH_2
111		$-\text{CH}_2-$		1	H	H	OH
112		$-\text{CH}_2-$		1	H	5-F	NH_2

Table 1

Compound No.	A	X	Q	n	R1	R2	R3
113		-CH ₂ -		1	H	4-Cl	NH ₂
114		-CH ₂ -		1	H	H	OH
115		-CH ₂ -		1	H	H	OH
116		-CH ₂ -		1	H	4-OH	OH
117		-CH ₂ -		1	H	H	OH
118		-CH ₂ -		1	H	5-CH ₃	OH
119		-CH ₂ -		1	H	5-OCH ₃	OH
120		-CH ₂ -		1	H	H	NH ₂
121		-CH ₂ -		1	H	5-OCH ₃	NH ₂
122		-(CH ₂) ₃ -		0	H	5-F	NH ₂

Table 1

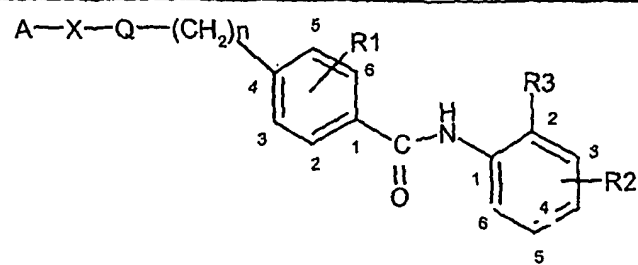
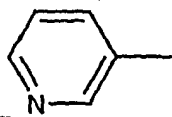
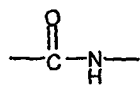
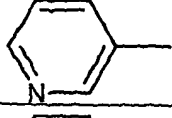
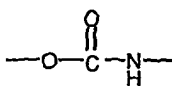
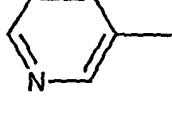
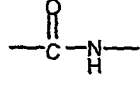
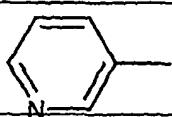

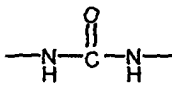
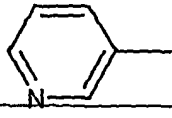

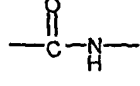
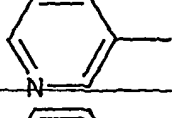
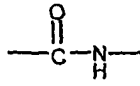
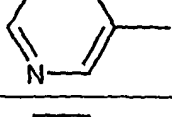
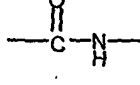
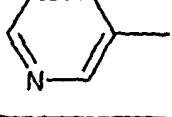
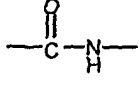
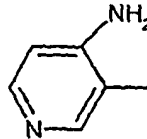
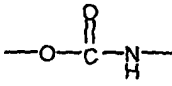
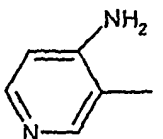
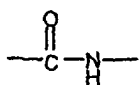
							
Compound No.	A	X	Q	n	R1	R2	R3
123		$-(CH_2)_2-$		0	3-Cl	H	NH ₂
124		$-(CH_2)_2-$		0	H	H	NH ₂
125		$-(CH_2)_2-$		1	H	H	OH
126				1	H	H	NH ₂
127				1	H	H	NH ₂
128		$-O-CH_2-$		1	2-Cl	H	NH ₂
129		$-O-CH_2-$		1	H	5-F	NH ₂
130		$-O-CH_2-$		1	H	5-OCH ₃	NH ₂
131		$-CH_2-$		1	H	H	NH ₂
132		$-O-CH_2-$		1	H	H	NH ₂

Table 1

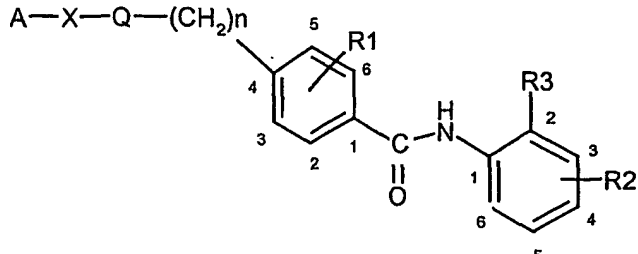
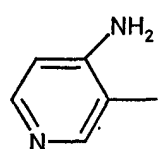
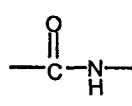
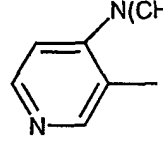
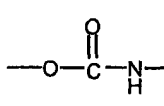
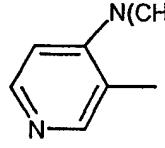
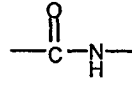
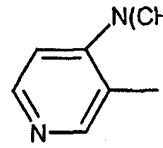
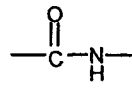
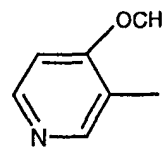
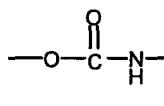
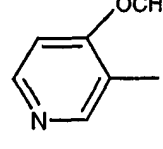
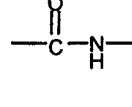
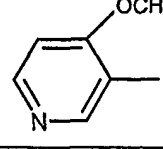
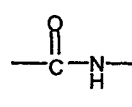
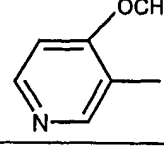
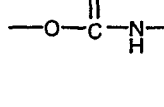
							
Compound No.	A	X	Q	n	R1	R2	R3
133		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂
134		-CH ₂ -		1	H	H	NH ₂
135		-O-CH ₂ -		1	H	H	NH ₂
136		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂
137		-CH ₂ -		1	H	H	NH ₂
138		-O-CH ₂ -		1	H	H	NH ₂
139		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂
140		-CH ₂ -		1	H	5-F	NH ₂

Table 1

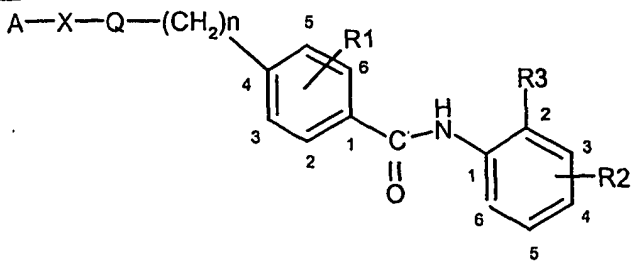
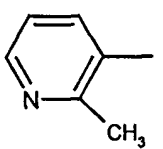
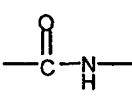
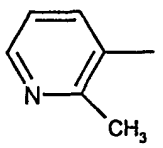
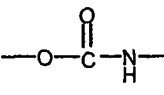
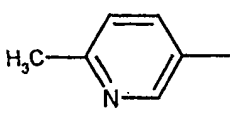
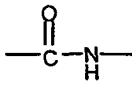
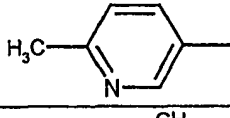
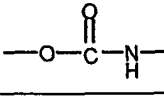
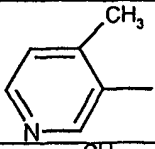
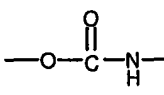
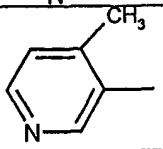
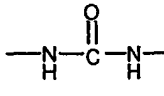
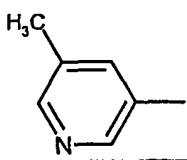
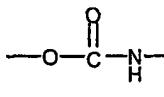
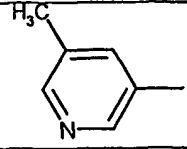
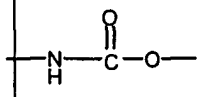
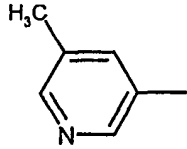
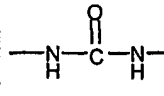
							
Compound No.	A	X	Q	n	R1	R2	R3
141		Direct bond		1	H	H	NH ₂
142		-CH ₂ -		1	H	H	NH ₂
143		Direct bond		1	H	H	NH ₂
144		-CH ₂ -		1	H	H	NH ₂
145		-CH ₂ -		1	H	H	NH ₂
146		-CH ₂ -		1	H	H	NH ₂
147		-CH ₂ -		1	H	H	NH ₂
148		-CH ₂ -		1	H	H	NH ₂
149		-CH ₂ -		1	H	H	NH ₂

Table 1

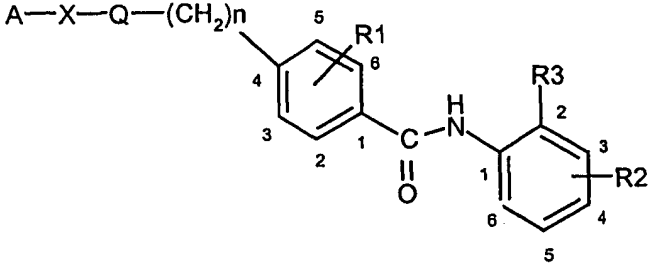
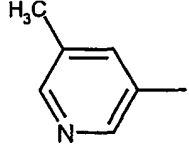
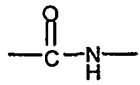
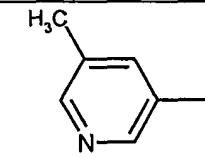
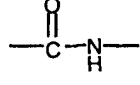
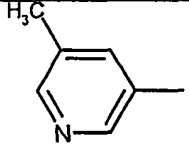
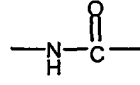
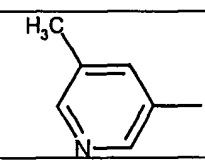
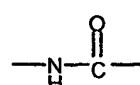
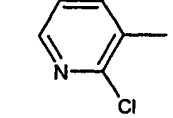
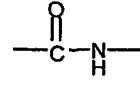
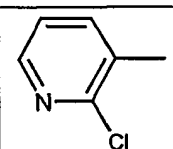
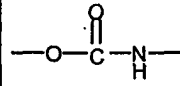
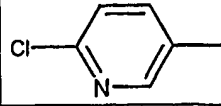
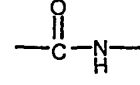
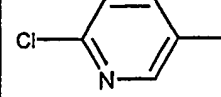
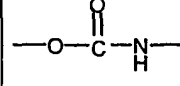
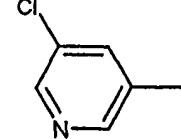
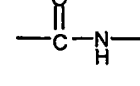
							
Compound No.	A	X	Q	n	R1	R2	R3
150		$-(CH_2)_2-$		1	H	H	NH ₂
151		$-(CH_2)_2-$		1	H	H	NH ₂
152		$-(CH_2)_2-$		1	H	H	NH ₂
153		$-CH_2-$		1	H	H	NH ₂
154		Direct bond		1	H	H	NH ₂
155		$-CH_2-$		1	H	H	NH ₂
156		Direct bond		1	H	H	NH ₂
157		$-CH_2-$		1	H	H	NH ₂
158		$-O-CH_2-$		1	H	H	NH ₂

Table 1

Compound No.	A	X	Q	n	R1	R2	R3
159		-O-CH ₂ -		1	H	H	NH ₂
160		-CH ₂ -		1	H	H	NH ₂
161		-CH ₂ -		1	H	H	NH ₂
162		-CH ₂ -		1	H	H	NH ₂
163		-CH ₂ -		1	H	H	NH ₂
164		-(CH ₂) ₂ -		1	H	H	NH ₂
165		-(CH ₂) ₂ -		1	H	H	NH ₂
166		-(CH ₂) ₂ -		0	H	H	NH ₂
167		-CH ₂ -		2	H	H	NH ₂

Table 1

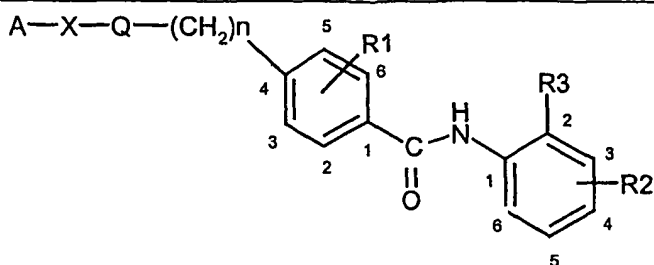
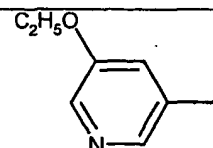
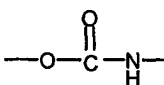
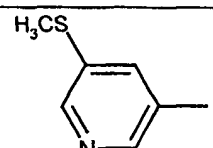
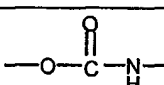
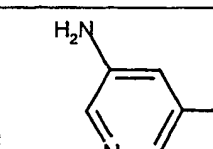
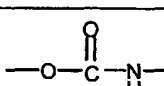
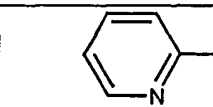
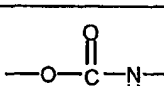
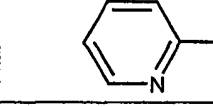
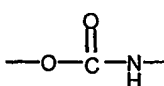
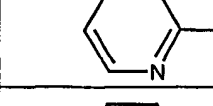
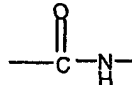
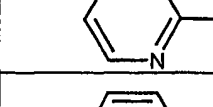
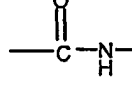
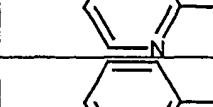
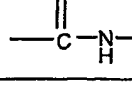
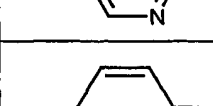
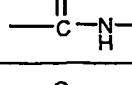
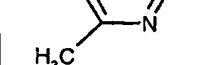
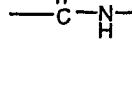
							
Compound No.	A	X	Q	n	R1	R2	R3
168		-CH ₂ -		1	H	H	NH ₂
169		-CH ₂ -		1	H	H	NH ₂
170		-CH ₂ -		1	H	H	NH ₂
171		-CH ₂ -		1	H	H	NH ₂
172		-(CH ₂) ₂ -		1	H	H	NH ₂
173		Direct bond		1	H	H	NH ₂
174		-CH ₂ -		0	H	H	NH ₂
175		-O-CH ₂ -		1	H	5-OCH ₃	NH ₂
176		-CH ₂ -O-CH ₂ -		0	H	H	NH ₂
177		-CH ₂ -		0	H	H	NH ₂

Table 1

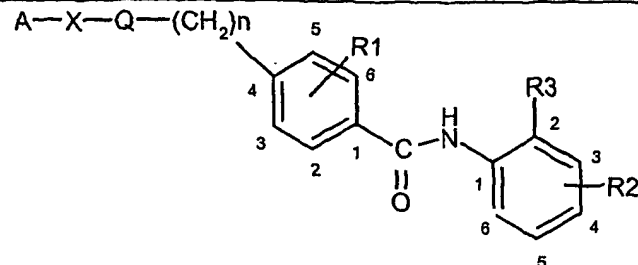
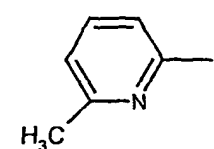
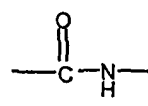
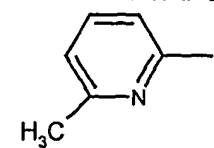
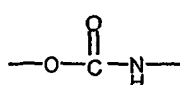
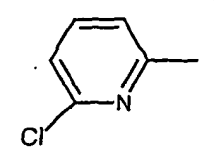
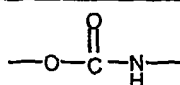
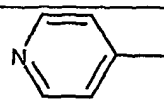
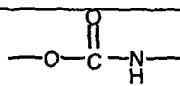
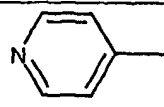
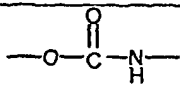
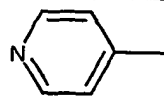
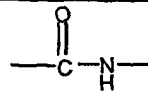
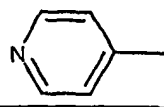
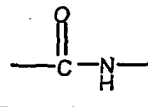
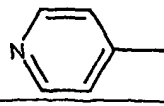
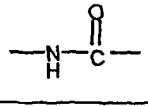
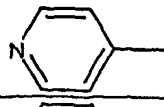
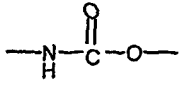
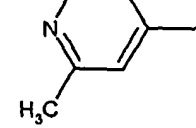
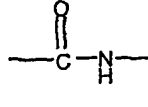
							
Compound No.	A	X	Q	n	R1	R2	R3
178		Direct bond		1	H	H	NH ₂
179		-CH ₂ -		1	H	H	NH ₂
180		-CH ₂ -		1	H	H	NH ₂
181		-CH ₂ -		1	H	H	NH ₂
182		-(CH ₂) ₂ -		1	H	H	NH ₂
183		Direct bond		1	H	H	NH ₂
184		-CH ₂ -		0	H	H	NH ₂
185		-CH ₂ -		0	H	H	NH ₂
186		-CH ₂ -		1	H	H	NH ₂
187		-CH ₂ -		0	H	H	NH ₂

Table 1

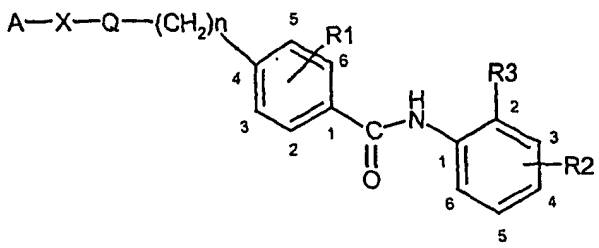
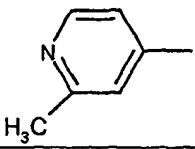
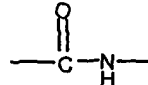
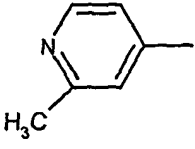
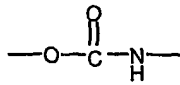
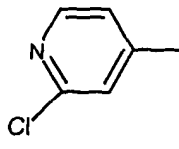
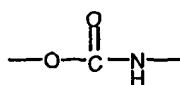
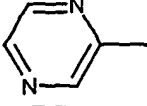
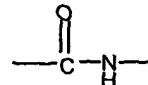
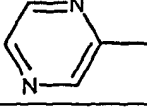
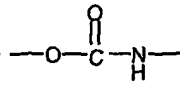
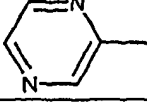
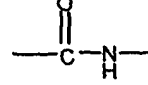
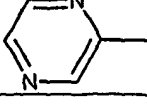
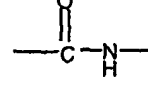
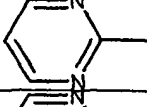
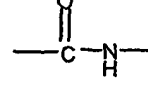
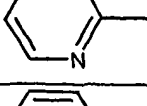
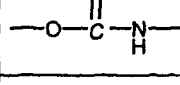
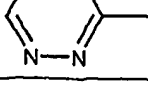
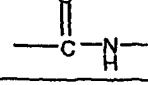
							
Compound No.	A	X	Q	n	R1	R2	R3
188		Direct bond		1	H	H	NH ₂
189		-CH ₂ -		1	H	H	NH ₂
190		-CH ₂ -		1	H	H	NH ₂
191		Direct bond		1	H	H	NH ₂
192		-CH ₂ -		1	H	H	NH ₂
193		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂
194		-CH ₂ -O-CH ₂ -		0	H	H	NH ₂
195		Direct bond		1	H	H	NH ₂
196		-CH ₂ -		1	H	H	NH ₂
197		Direct bond		1	H	H	NH ₂

Table 1

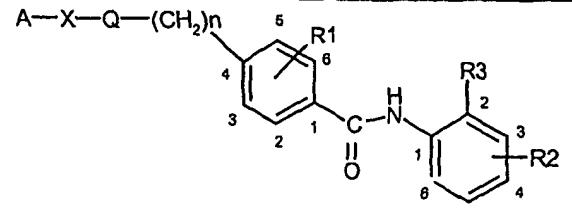
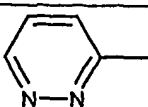
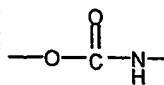
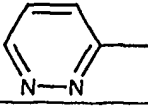
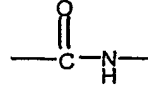
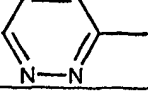
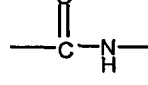
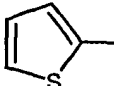
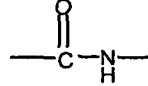
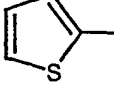
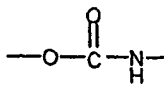
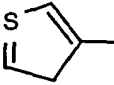
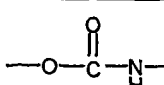
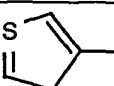
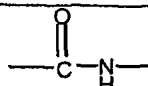
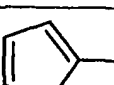
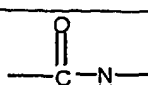
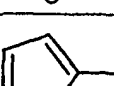
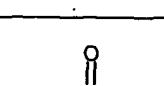
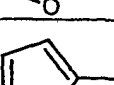
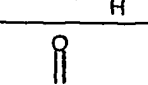

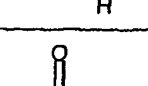
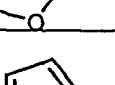
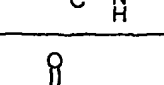
							
Compound No.	A	X	Q	n	R1	R2	R3
198		-CH ₂ -		1	H	H	NH ₂
199		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂
200		-CH ₂ -O-CH ₂ -		0	H	H	NH ₂
201		Direct bond		1	H	H	NH ₂
202		-CH ₂ -		1	H	H	NH ₂
203		-(CH ₂) ₂ -		1	H	H	NH ₂
204		-CH ₂ -O-CH ₂ -		0	H	H	NH ₂
205		Direct bond		1	H	H	NH ₂
206		-CH ₂ -		1	H	H	NH ₂
207		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂
208		-CH ₂ -O-CH ₂ -		0	H	H	NH ₂
209		Direct bond		1	H	H	NH ₂

Table 1

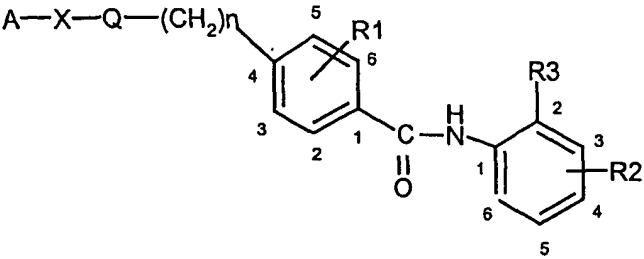
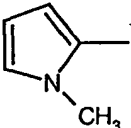
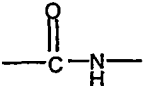
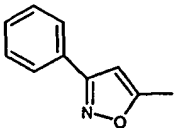
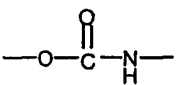
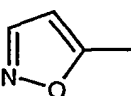
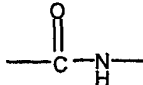
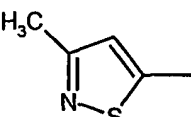
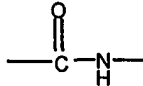
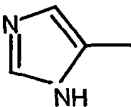
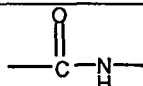
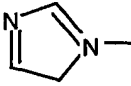
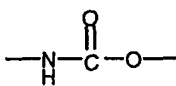
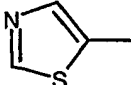
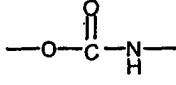
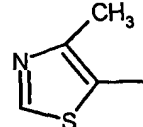
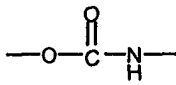
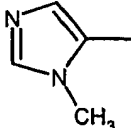
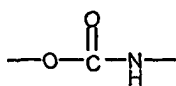
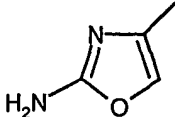
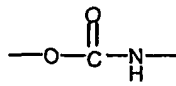
							
Compound No.	A	X	Q	n	R1	R2	R3
210		Direct bond		1	H	H	NH ₂
211		-CH ₂ -		1	H	H	NH ₂
212		Direct bond		1	H	H	NH ₂
213		Direct bond		1	H	H	NH ₂
214		Direct bond		1	H	H	NH ₂
215		-(CH ₂) ₃ -		1	H	H	NH ₂
216		-CH ₂ -		1	H	H	NH ₂
217		-(CH ₂) ₂ -		1	H	H	NH ₂
218		-CH ₂ -		1	H	H	NH ₂
219		-CH ₂ -		1	H	H	NH ₂

Table 1

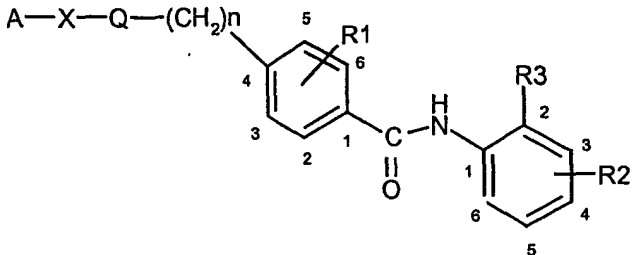
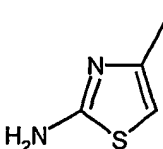
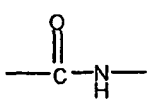
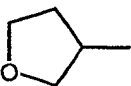
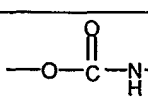
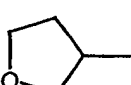
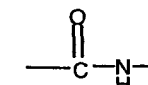
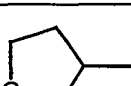
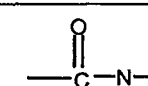
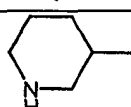
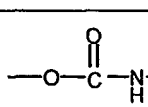
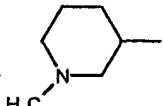
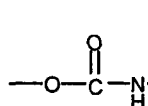
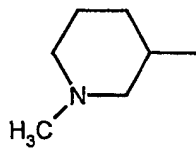
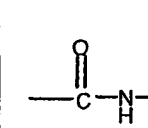
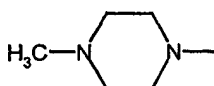
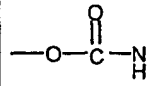
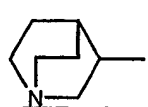
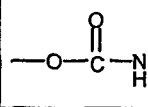
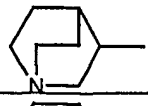
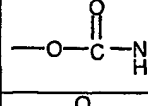
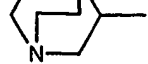
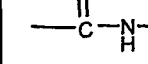
							
Compound No.	A	X	Q	n	R1	R2	R3
220		-CH ₂ -		1	H	H	NH ₂
221		-CH ₂ -		1	H	H	NH ₂
222		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂
223		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂
224		Direct bond		1	H	H	NH ₂
225		-CH ₂ -		1	H	H	NH ₂
226		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂
227		-(CH ₂) ₃ -		1	H	H	NH ₂
228		Direct bond		1	H	H	NH ₂
229		-CH ₂ -		1	H	H	NH ₂
230		-CH ₂ -O-CH ₂ -		1	H	H	NH ₂

Table 1

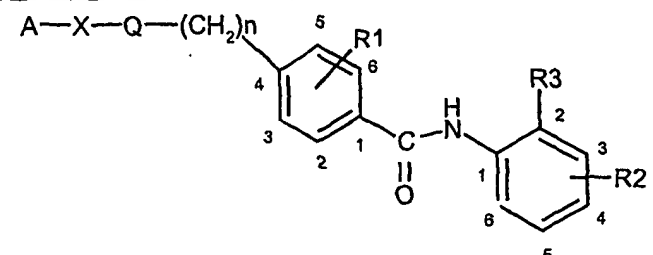
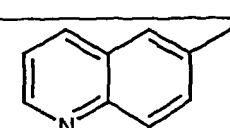
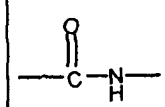
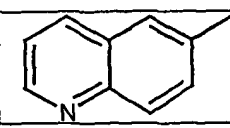
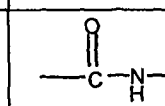
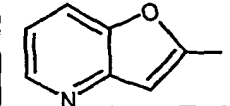
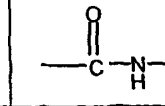
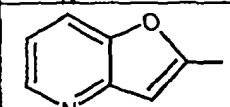
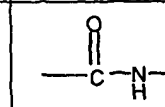
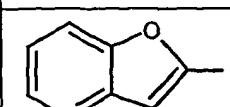
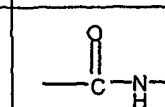
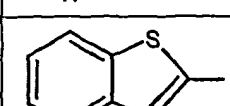
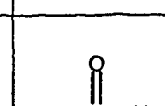
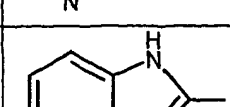
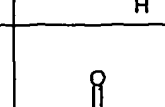
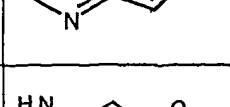
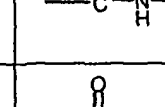
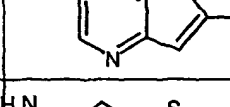
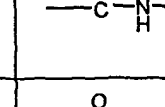
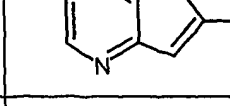
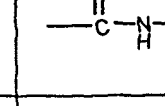
							
Compound No.	A	X	Q	n	R1	R2	R3
231		Direct bond		1	H	H	NH ₂
232		Direct bond		1	H	H	NH ₂
233		Direct bond		1	H	H	NH ₂
234		Direct bond		1	H	H	NH ₂
235		Direct bond		1	H	H	NH ₂
236		Direct bond		1	H	H	NH ₂
237		Direct bond		1	H	H	NH ₂
238		Direct bond		1	H	H	NH ₂
239		Direct bond		1	H	H	NH ₂
240		Direct bond		1	H	H	NH ₂

Table 2

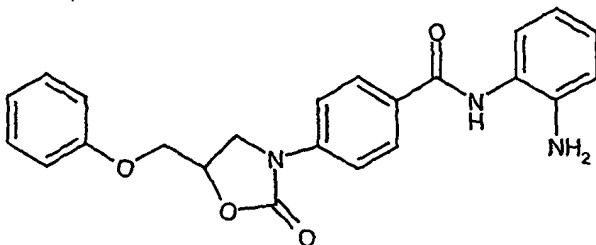
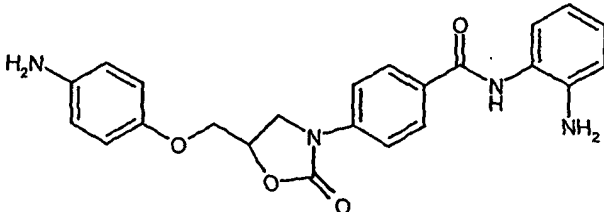
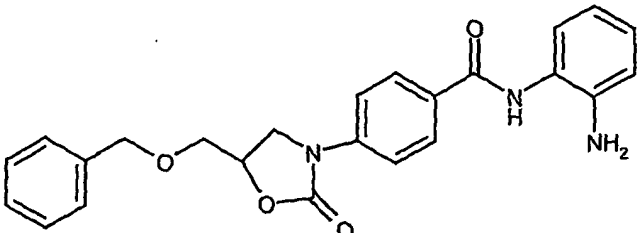
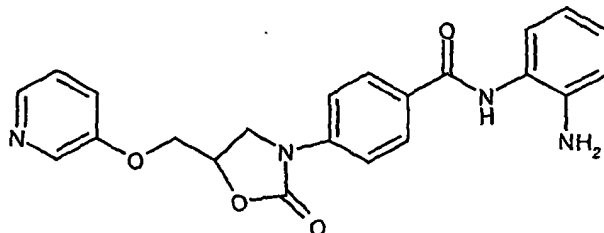
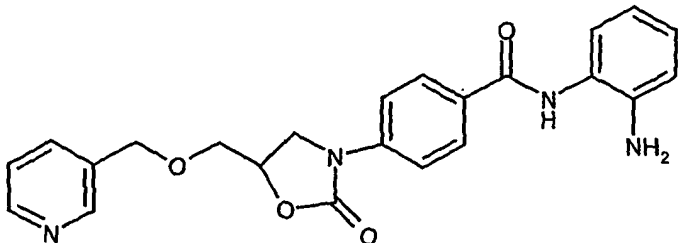
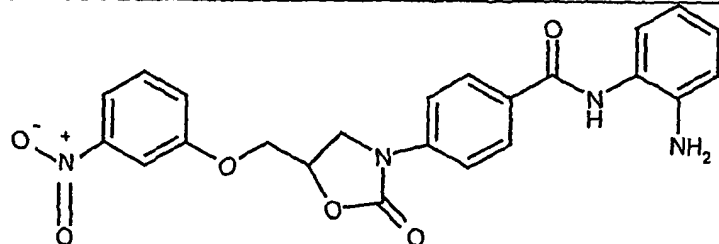
Compound No.	Structural formula
1	
2	
3	
4	
5	
6	

Table 2

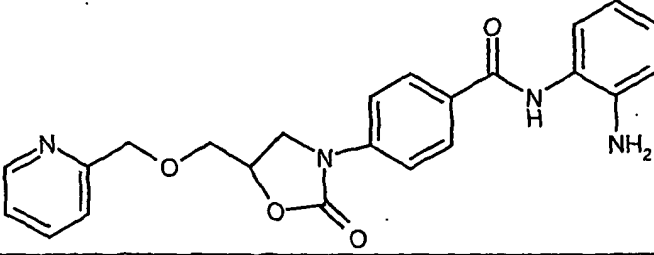
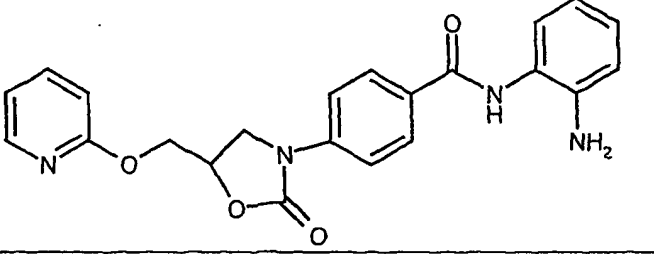
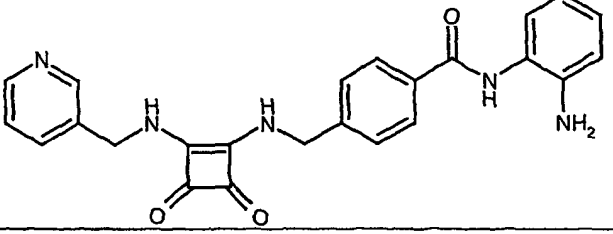
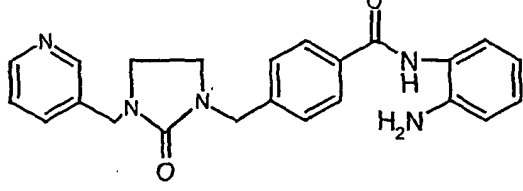
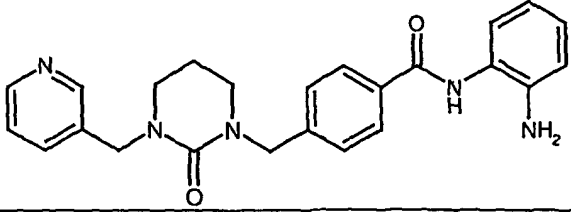
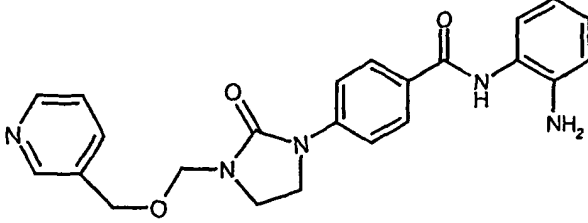
Compound No.	Structural formula
7	
8	
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11	
12	

Table 2

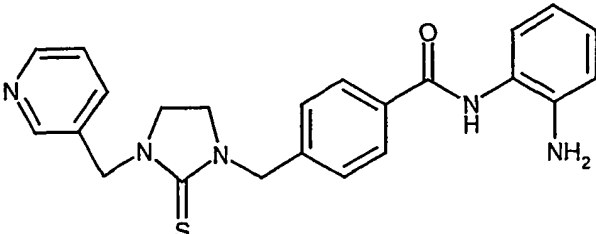
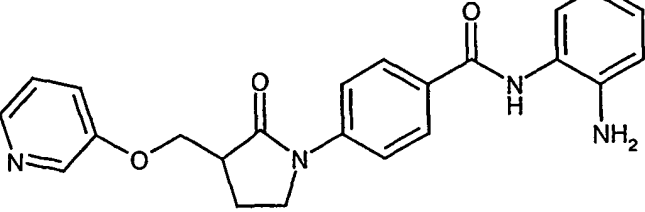
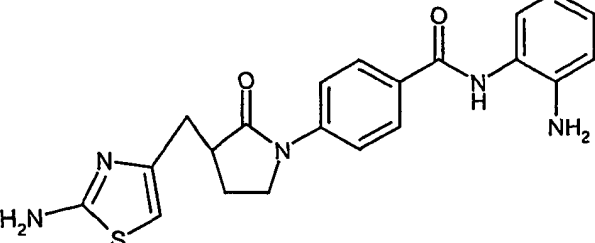
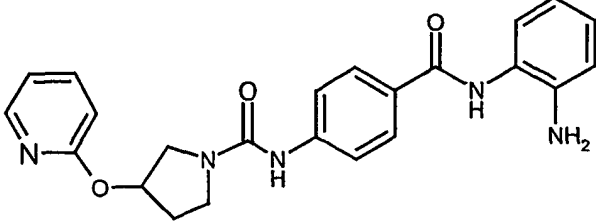
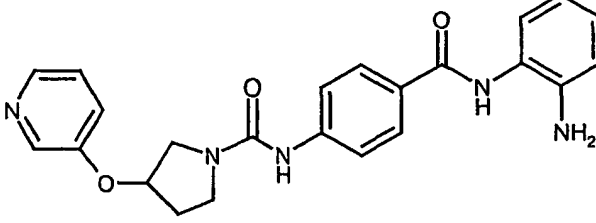
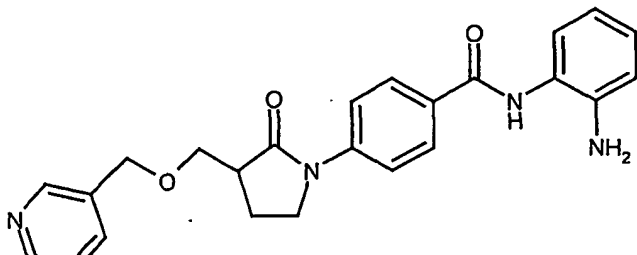
Compound No.	Structural formula
13	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)CN3CC(S)CC3Cc4cccnc4</chem>
14	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)COc3ccncc3</chem>
15	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)CN3CC(=O)CC3Cc4ccsc4N</chem>
16	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)C(=O)N3CCOC3c4ccncc4</chem>
17	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)C(=O)N3CCOC3c4ccncc4</chem>
18	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)CN3CC(=O)CC3COc4cccnc4</chem>

Table 2

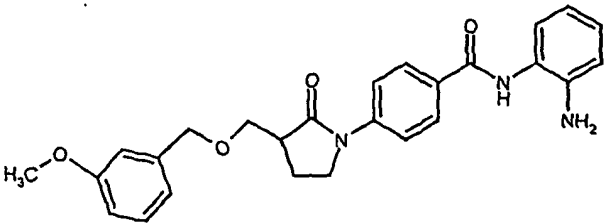
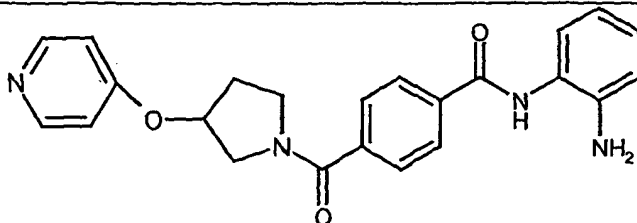
Compound No.	Structural formula
19	
20	

Table 3

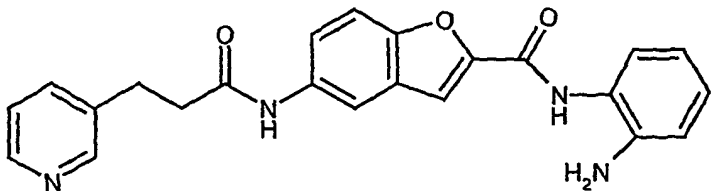
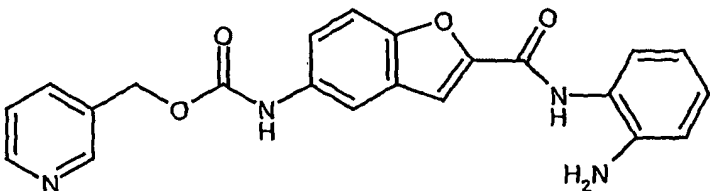
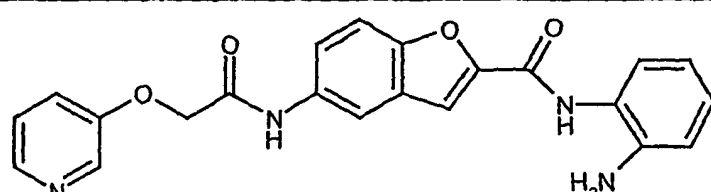
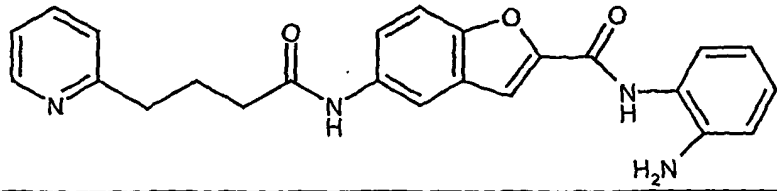
Compound No.	Structural formula
1	
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Table 3

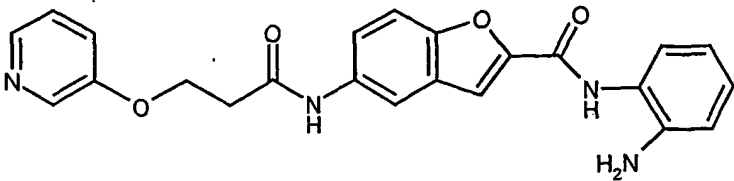
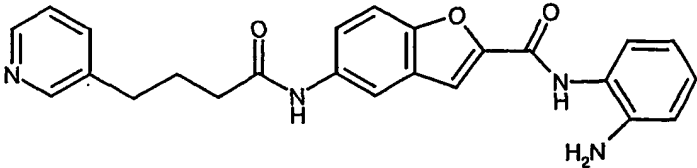
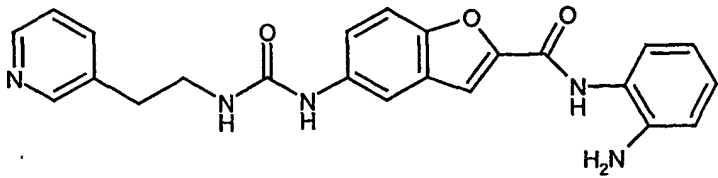
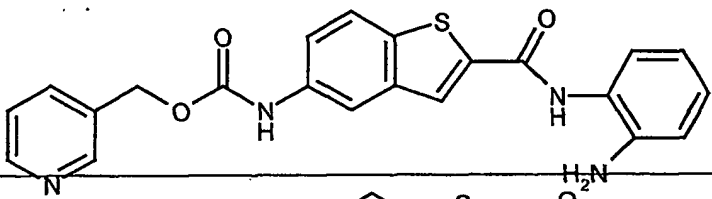
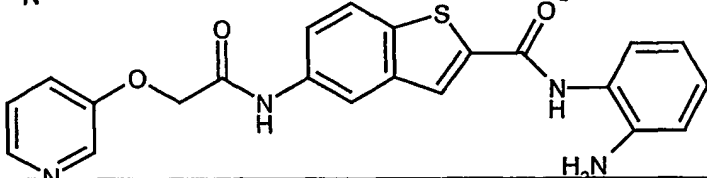
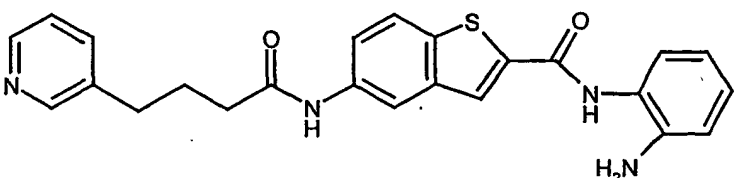
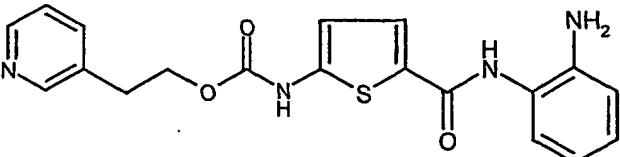
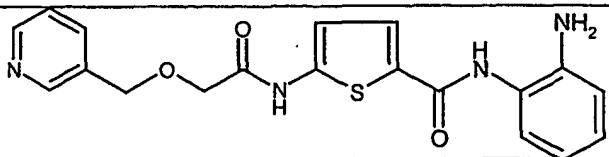
Compound No.	Structural formula
5	
6	
7	
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10	
11	
12	

Table 3

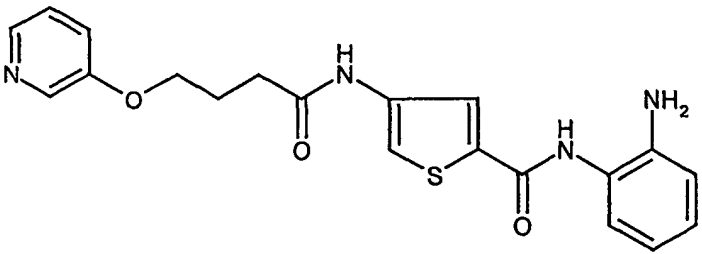
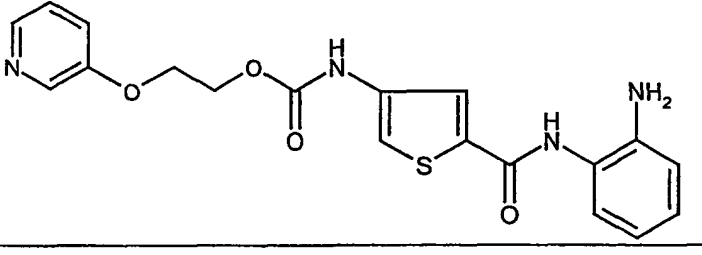
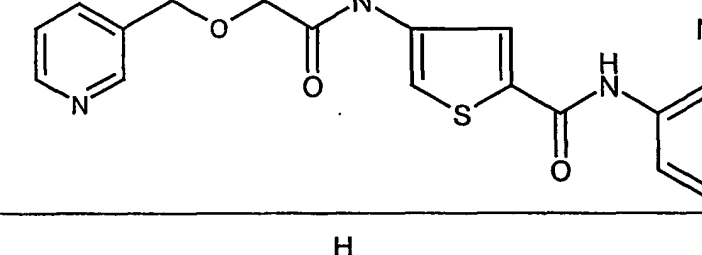
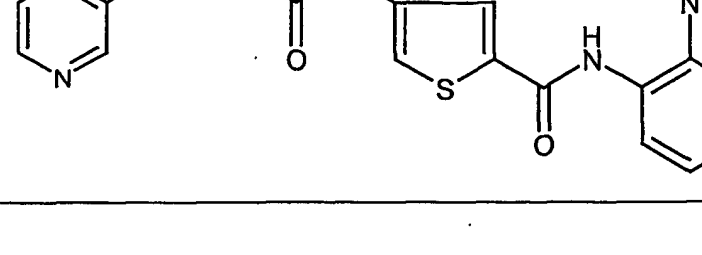
Compound No.	Structural formula
13	
14	
15	
16	

Table 4

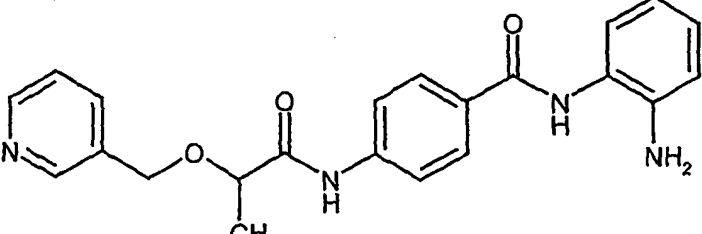
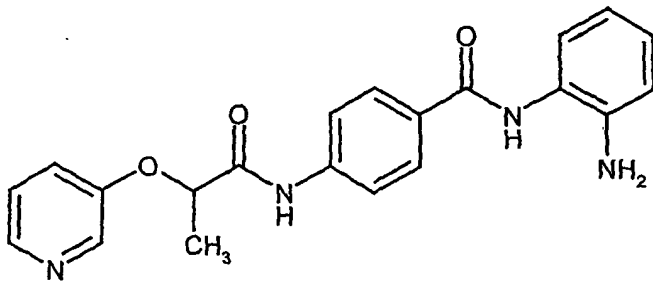
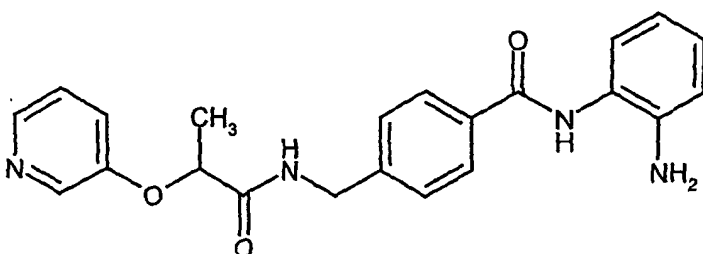
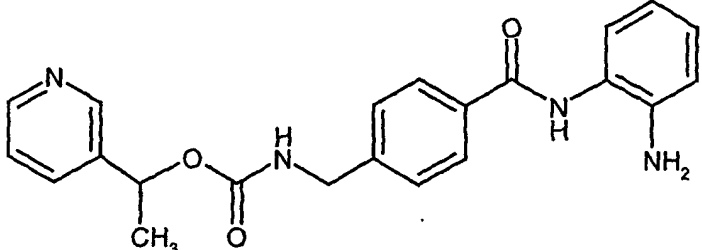
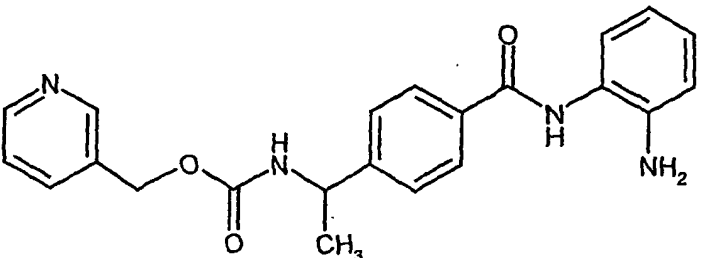
Compound No.	Structural formula
1	 <chem>NC1=CC=C(C=C1)NC(=O)C2=CC=CC=C2NC(=O)C(C)OCc3ccncc3</chem>
2	 <chem>NC1=CC=C(C=C1)NC(=O)C2=CC=CC=C2NC(=O)C(C)Oc3ccncc3</chem>
3	 <chem>NC1=CC=C(C=C1)NC(=O)C2=CC=CC=C2NC(=O)C(C)Oc3ccncc3</chem>
4	 <chem>NC1=CC=C(C=C1)NC(=O)C2=CC=CC=C2NC(=O)C(C)Oc3ccncc3</chem>
5	 <chem>NC1=CC=C(C=C1)NC(=O)C2=CC=CC=C2NC(=O)C(C)OCc3ccncc3</chem>

Table 4

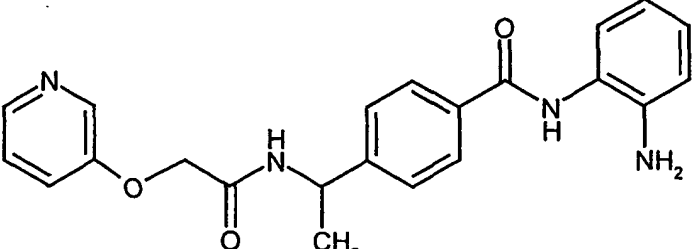
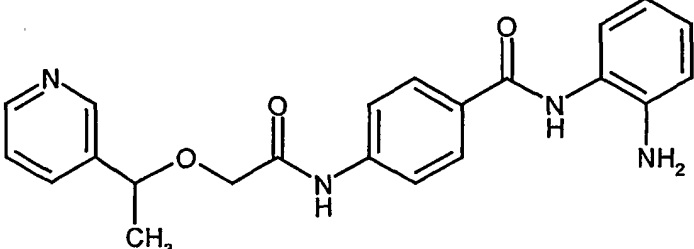
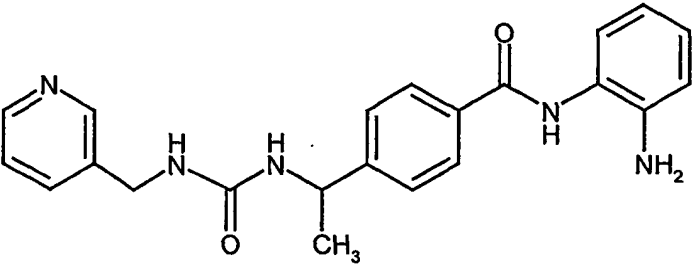
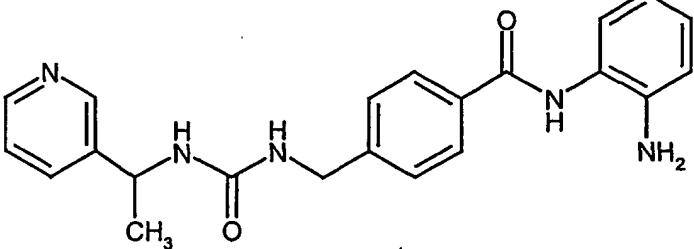
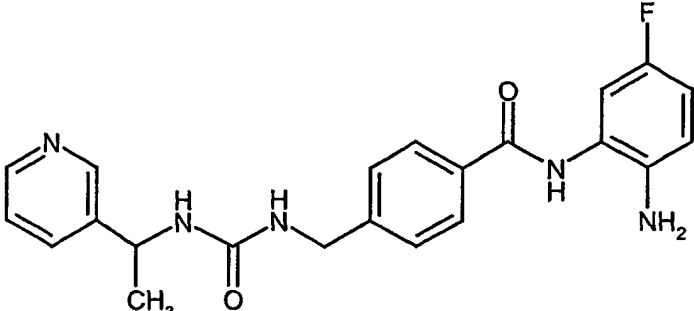
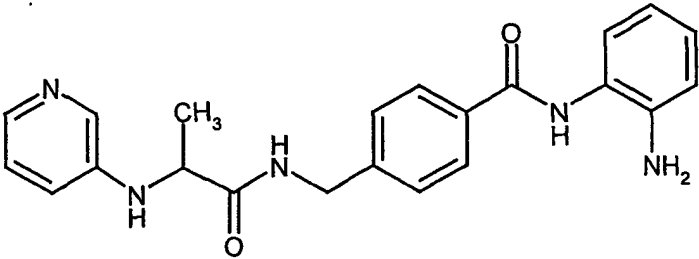
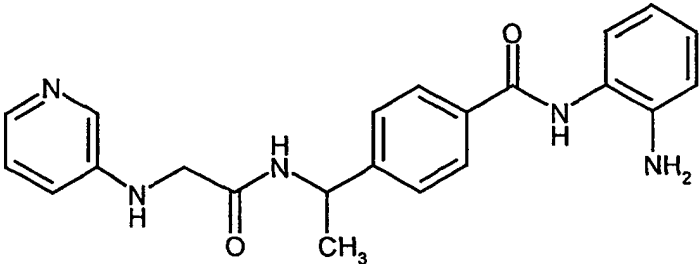
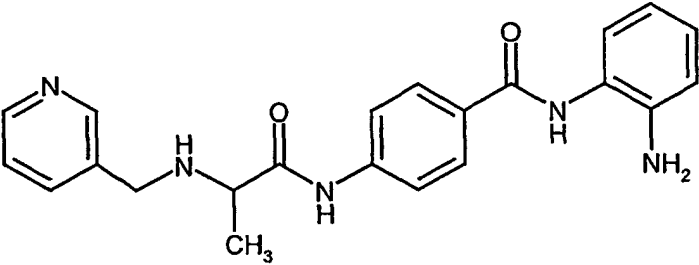
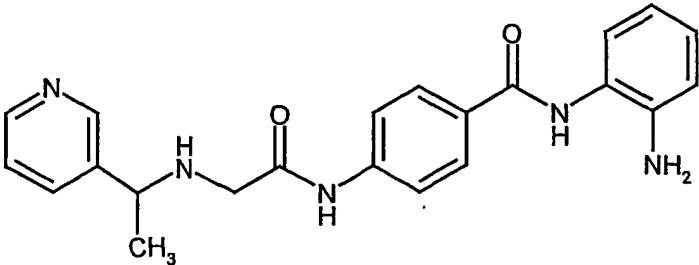
Compound No.	Structural formula
6	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)C(C)NC(=O)COc3ccncc3</chem>
7	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)C(C)NC(=O)COc3ccncc3</chem>
8	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)C(C)NC(=O)COc3ccncc3</chem>
9	 <chem>Nc1ccccc1NC(=O)c2ccc(cc2)C(C)NC(=O)COc3ccncc3</chem>
10	 <chem>Nc1cc(F)ccc1NC(=O)c2ccc(cc2)C(C)NC(=O)COc3ccncc3</chem>

Table 4

Compound No.	Structural formula
11	
12	
13	
14	

The compounds of this invention may be prepared as described in US 6,174,905.

Examples for compound b) of the instant inventive combination are described as follows:

- 5 It should however be noted that these examples do not limit the inventive combination only to these compounds b).

Example b-1

- 10 Preparation of N-(2-aminophenyl)-4-(N-benzoylaminomethyl)benzamide hydrochloride (Table 1: hydrochloride of Compound 1):

Process 1-1

- 15 To a suspension of 21.16 g of 4-aminomethylbenzoic acid(140 mmol) in 450 ml of dichloromethane was added 42 ml of triethylamine (300 mmol). Under ice-cooling, 60.4 g of trifluoroacetic anhydride (287 mmol) in 50 ml of dichloromethane were added dropwise, maintaining the inner temperature at 3 to 8 °C., and then the mixture was stirred four 3 hours. The reaction mixture
20 was poured into a saturated aqueous sodium bicarbonate solution, and was acidified with 10% hydrochloric acid. The gel precipitatem was collected by filtration and dried to give 30.4 g of 4-(N-trifluoroacetylaminomethyl)benzoic acid (Yield: 87.8%) as an opalescent solid.
- 25 ¹ H NMR (270 MHz, DMSO-d₆) . δ. ppm: 4.47(2H, d, J=5.8 Hz), 7.39(2H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 10.08(1H, t, J=5.8 Hz), 12.95(1H, br.s.)

Process 1-2

- 30 To a solution of 108 g of o-phenylenediamine (1.0 mol) in 1000 ml of dioxane was added 500 ml of 1N sodium hydroxide aq., and then 218 g of tert-butylidicarbonate (1.1 mol) in 500 ml of dioxane under ice-cooling. After stirring

for 6 hours at room temperature, the mixture was left overnight. The mixture was concentrated to 1/2 volume by evaporation, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography (eluent: 5 chloroform) to give a solid, which was then washed with diethyl ether to give 68.4 g of N-tert-butoxycarbonyl-o-phenylenediamine (Yield: 32.8%) as a white solid.

¹ H NMR(270 MHz, CDCl₃) .δ. ppm: 1.51(9H, s), 3.75(2H, s), 6.26(1H, s), 10 6.77(1H, d, J=8.1 Hz), 6.79(1H, dd, J=7.3, 8.1 Hz), 7.00(1H, dd, J=7.3, 8.1 Hz), 7.27(1H, d, J=8.1 Hz)

Process 1-3

15 To a suspension of 30 g of the compound from the process (1-1) (121 mmol) in 200 ml of dichloromethane were slowly added dropwise 21 g of oxalyl chloride (165 mmol) with intermittently adding DMF (0.1 ml per 2 ml addition), maintaining the inner temperature within 10 to 15 °C by ice-cooling. After completion of the addition, the mixture was stirred until bubble generation 20 ceased, and then at 40 °C. for an additional hour. After evaporation, excess oxalyl chloride was azeotropically removed with toluene, and then the residue was redissolved in 100 ml of dichloroethane. The prepared acid chloride solution was added dropwise to a solution of 22.88 g of the compound from the process (1-2) (110 mmol) in 100 ml of dichloromethane and 200 ml of pyridine, 25 maintaining the inner temperature within 7 to 9 °C. by ice-cooling.

After addition, the mixture was warmed to room temperature, and was left overnight. After adding saturated sodium bicarbonate aq. to the reaction mixture, the resulting mixture was extracted with chloroform, and the organic 30 layer was washed with saturated brine, dried and evaporated. To the residue was added methanol-diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 28.1 g of N-([2-(N-tert-butoxycarbonyl)amino-

phenyl]-4-(N-trifluoroacetylaminomethyl) benzamide (Yield: 58%) as a light yellow solid.

¹ H NMR (270 MHz, DMSO-d₆) .delta. ppm: 1.44(9H, s), 4.48(2H, d, J=5.9 Hz),
5 7.12-7.23(2H, m), 7.44(2H, d, J=8.1 Hz), 7.54(2H, d, J=8.1 Hz) 7.94(2H, d, J=8.1 Hz), 8.68(1H, br.s), 9.83(1H, s), 10.10(1H, br.t, J=5.9 Hz)

Process 1-4

- 10 To a suspension of 13.12 g of the compound from the process (1-3) (30 mmol) in 120 ml of methanol and 180 ml of water were added 4.70 g of potassium carbonate (34.0 mmol), and the mixture was heated with stirring at 70 °C. for 4 hours. It was extracted with chloroform, and the organic layer was washed with saturated brine, dried, evaporated and dried to give 10.3 g of 4-aminomethyl-N-
15 [2-(N-tertbutoxycarbonyl)aminophenyl]benzamide (Yield: quantitative) as a light yellow amorphous solid.

¹ H NMR (270 MHz, DMSO-d₆) .delta. ppm: 3.80(2H, s), 7.13-7.23(2H, m), 7.48-7.58(4H, m), 7.90(2H, d, J=8.1 Hz), 8.69(1H, br.s), 9.77(1H, br.s)

20

Process (1-5)

- To a solution of 0.11 g of the compound from the process (1-4) (0.44 mmol) in 5 ml of pyridine was added 0.08 g of benzoyl chloride (0.53 mmol), and the
25 mixture was gradually warmed to room temperature and then stirred for 8 hours. Saturated sodium bicarbonate aq. was added, and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with diisopropyl ether, and the solid obtained was dried to give 0.14 g of N-[2-(N-tert-
30 butoxycarbonyl)aminophenyl]-4-(N-benzoylaminomethyl)benzamide (Yield: 71.4%) as a white solid.

¹ H NMR (270 MHz, DMSO-d₆) .delta. ppm: 1.44(9H, s), 4.56(2H, d, J=5.9 Hz), 7.11-7.22(2H, m), 7.46-7.56(7H, m), 7.90-7.94(4H, m), 8.67(1H, s), 9.15(1H, t, J=5.9 Hz), 9.81(1H, s)

5 Process (1-6)

To a solution of 0.10 g of the compound from the process (1-5) (0.224 mmol) in 5 ml of dioxane and 1 ml of methanol was added 5 ml of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 7 hours. To the
10 residue after evaporation was added diisopropyl ether, and the formed solid was collected by filtration and dried to give 0.08 g of N-(2-aminophenyl)-4-(N-benzoylaminomethyl)benzamide hydrochloride (Yield: 93%) as a light brown solid.

15 mp: 206-209 °C.

¹ H NMR (270 MHz, DMSO-d₆) .delta. ppm: 4.57(2H, d, J=5.8 Hz), 7.27-7.38(4H, m), 7.47-7.59(5H, m), 7.92(1H, d, J=8.1 Hz), 8.05(1H, d, J=8.1 Hz), 9.19(1H, t, J=5.8 Hz), 10.38(1H, br.s)

20

IR(KBr, cm⁻¹): 3286, 3003(br.), 1630, 1551, 1492, 1306, 1250, 749, 695.

As described in Example 1, the compounds of Examples 2 to 44 were prepared, each of whose melting point (mp), ¹ H NMR data and/or IR data are described
25 below.

Example 2

N-(2-aminophenyl)-4-[N-(2-chlorobenzoyl)aminomethyl]benzamide (Table 1: Compound 14)

5

mp: 201-204 °C. (dec.)

¹ H NMR (270 MHz, DMSO-d₆) .delta. ppm: 4.52(2H, t, J=5.9 Hz), 4.89(2H, br.s), 6.60(1H, ddd, J=1.5, 7.3, 8.1 Hz), 6.78(1H, dd, J=1.5, 8.1 Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.17(1H, d, J=8.1 Hz), 7.38-7.54(6H, m), 7.97(2H, d, J=8.1 Hz), 9.06(1H, br.t, J=5.9 Hz), 9.63(1H, br.s)

10

IR (KBr) cm⁻¹ : 3268, 1649, 1458, 1304, 748

15

Example 3

N-(2-aminophenyl)-4-[N-(2-nitrobenzoyl)aminomethyl]benzamide hydrochloride (Table 1: hydrochloride of Compound 18)

20

mp: 210-212 °C.(dec.)

¹ H NMR(270 MHz, DMSO-d₆) ppm: 4.55(2H, t, J=5.9 Hz), 7.20-7.40(3H, m), 7.50-7.60(1H, m), 7.53(2H, d, J=8.1 Hz), 7.60-7.70(2H, m), 7.83(1H, ddd, J=1.5, 8.1, 8.1 Hz), 8.00-8.10(3H, m), 9.34(1H, t, J=5.9 Hz), 10.43(1H, br.s)

25

IR(KBr)cm⁻¹ : 3283, 2500-3000(br.), 1648, 1534, 1461, 1362, 1314, 754, 701

30

Example 4

N-(2-aminophenyl)-4-[N-(4-methylbenzoyl)aminomethyl]benzamide
hydrochloride (Table 1: hydrochloride of Compound 28)

5

mp: (amorphous).

^1H NMR (270 MHz, DMSO- d_6) δ , ppm: 2.37(3H, s), 4.56(2H, d, J=5.0 Hz),
7.20-7.30(6H, m), 7.47(4H, d, J=8.8 Hz), 7.82(2H, d, J=8.8 Hz), 8.03(2H, d,
10 J=8.8 Hz), 9.09(1H, t, J=5 Hz), 10.36(1H, br.s)

IR(KBr) cm^{-1} : 3269(br.), 2861(br.), 1743, 1636, 1534, 1505, 1456, 1308, 1120,
753.

15

Example 5

N-(2-aminophenyl)-4-[N-(3-methoxybenzoyl)aminomethyl]benzamide (Table 1:
Compound 30)

20

mp: 182-185 °C.

^1H NMR(270 MHz, DMSO- d_6) δ , ppm: 3.81(3H, s), 4.54(2H, d, J=5.9 Hz),
4.88(2H, br.s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd,
25 J=6.6, 7.3 Hz), 7.11(1H, dd, J=1.5, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.35-
7.51(5H, m), 7.94(2H, d, J=8.1 Hz), 9.12(1H, br.t, J=5.9 Hz), 9.63(1H, br.s)

IR(KBr) cm^{-1} : 3301, 1637, 1524, 1489, 1457, 1314, 1248, 752

30

Example 6

N-(2-aminophenyl)-4-[N-(4-methoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 31)

5

mp: 149-151 °C.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.82(3H, s), 4.53(2H, d, J=5.9 Hz), 4.88(2H, s), 6.59(1H, dd, J=7.3, 7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.94-7.00(1H, m), 7.02(2H, d, J=8.8 Hz), 7.16(1H, d, J=8.1 Hz), 7.43(2H, d, J=8.1 Hz), 7.89(2H, d, J=8.8 Hz), 7.94(2H, d, J=8.1 Hz), 8.98(1H, br.t, J=5.9 Hz), 9.61(1H, br.s)

15

IR(KBr)cm⁻¹ : 3297, 1630, 1527, 1505, 1457, 1256, 1177, 1024, 843, 749

Example 7

N-(2-aminophenyl)-4-[N-(3,4,5-trimethoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 33)

20

mp: 208-210 °C.(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.71(3H, s), 3.83(6H, s), 4.55(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.26(2H, s), 7.44(2H, d, J=8.1 Hz), 7.95(2H, d, J=8.8 Hz), 9.07(1H, t, J=5.9 Hz), 9.62(1H, br.s)

25

IR(KBr)cm⁻¹ : 3267, 1635, 1582, 1457, 1237, 1132, 755

30

Example 8

N-(2-aminophenyl)-4-[N-[4-(N,N-dimethyl)aminobenzoyl]aminomethyl]benzamide (Table 1: Compound 36)

5

mp: 216-219°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.98(6H, s), 4.51(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=8.1, 8.1 Hz), 6.71(2H, d, J=8.8 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.41(2H, d, J=8.1 Hz), 7.78(2H, d, J=8.8 Hz), 7.93(2H, d, J=8.1 Hz), 8.77(1H, t, J=5.9 Hz), 9.63(1H, br.s).

10

IR(KBr)cm⁻¹ : 3301, 1632, 1519, 1457, 1298, 754

15 Example 9

N-(2-aminophenyl)-4-[N-(4-trifluoromethylbenzoyl)aminomethyl]benzamide (Table 1: Compound 42)

20 mp: 243-246°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.58(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.59(1H, dd, J=6.6, 7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.94(1H, dd, J=5.9, 6.6 Hz), 7.16(1H, d, J=8.1 Hz), 7.45(2H, d, J=8.1 Hz), 7.88(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.1 Hz), 8.11(2H, d, J=8.1 Hz), 9.38(1H, t, J=5.9 Hz), 9.64 (1H, br.s)

25

IR(KBr)cm⁻¹ : 3301, 1640, 1549, 1523, 1458, 1334, 1162, 1120, 1070, 856, 750

30

Example 10

N-(2-aminophenyl)-4-[N-(4-carboxybenzoyl)aminomethyl]benzamide
hydrochloride (Table 1: hydrochloride of Compound 45)

5

mp: (amorphous).

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.58(2H, d, J=5.9 Hz), 7.29-
7.37(3H, m), 7.49(3H, d, J=8.1 Hz), 8.02-8.06(6H, m), 9.36(1H, t, J=5.9 Hz),
10 10.4(1H, br.s)

IR(KBr)cm⁻¹ : 3432(br.), 1718, 1637, 1542, 1499, 1303(br.), 1116, 1018, 757

Example 11

15

N-(2-aminophenyl)-4-[N-(4-methoxycarbonylbenzoyl)aminomethyl]benzamide
(Table 1: Compound 46)

mp: 204-209°C(dec.)

20

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.89(3H, s), 4.57(2H, d, J=5.9 Hz),
4.88(2H, br.s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(2H, d, J=7.3 Hz), 6.97(1H, ddd,
J=1.5, 6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.45 (2H, d, J=8.1 Hz), 7.95(2H, d,
J=8.1 Hz), 8.03(2H, d, J=8.8 Hz), 8.07(2H, d, J=8.8 Hz), 9.35(1H, t, J=5.9 Hz),
25 9.64(1H, br.s)

IR(KBr)cm⁻¹ : 3287(br.), 1721, 1634, 1281, 1113, 750, 703

30

Example 12

N-(2-aminophenyl)-4-(N-picolinoylaminomethyl)benzamide (Table 1: Compound 173)

5

mp: 173-178°C(dec.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.57(2H, d, J=6.6 Hz), 4.88(2H, br.s), 6.59(1H, dd, J=7.3, 8.1 Hz), 6.77(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.44(2H, d, J=8.1 Hz), 7.60-7.65(1H, m), 7.93(2H, d, J=8.1 Hz), 7.98-8.08(2H, m), 8.67(1H, d, J=4.4 Hz), 9.45(1H, t, J=6.6 Hz), 9.61(1H, br s)

10

IR(KBr)cm⁻¹ : 3330, 1656, 1634, 1523, 1456, 1294, 752

15

Example 13

N-(2-aminophenyl)-4-[N-(6-methylpicolinoyl)aminomethyl]benzamide (Table 1: Compound 178)

20

mp: 172-173°C

25

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.51(3H, s), 4.57(2H, d, J=6.6 Hz), 5.0(2H, br.s), 6.61(1H, dd, J=7.3, 8.1 Hz), 6.79(1H, d, J=7.3 Hz), 6.98(1H, dd, J=7.3, 8.1 Hz), 7.17(1H, d, J=7.3 Hz), 7.44(2H, d, J=8.1 Hz), 7.43-7.49(1H, m), 7.84-7.90(2H, m), 7.94(2H, d, J=8.1 Hz), 9.27(1H, t, J=5.9 Hz), 9.64(1H, br.s)

IR(KBr)cm⁻¹ : 3331, 1675, 1634, 1594, 1523, 1454, 1307, 1292, 750

30

Example 14

N-(2-aminophenyl)-4-(N-nicotinoylaminomethyl)benzamide (Table 1: Compound 71)

5

mp: 193-196°C

^1H NMR(270 MHz, DMSO- d_6) .delta. ppm: 4.58(2H, d), 4.88(2H, br.s), 6.60(1H, t), 6.78(1H, d), 6.97(1H, t), 7.16(1H, d), 7.46(2H, d), 7.53(1H, dd), 7.95(2H, d),
10 8.24(1H, ddd), 8.73(1H, dd), 9.07(1H, d), 9.32(1H, br.t), 9.63(1H, br.s)

IR(KBr)cm $^{-1}$: 3301, 1639, 1522, 1457, 1314, 749, 705

Example 15

15

N-(2-aminophenyl)-4-[N-(2-methylnicotinoyl)aminomethyl]benzamide (Table 1: Compound 141)

mp: 191-194°C(dec.

20

^1H NMR(270 MHz, DMSO- d_6) .delta. ppm: 2.53(3H, s), 4.53(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=6.6, 8.1 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.17(1H, d, J=7.3 Hz), 7.29(1H, dd, J=5.1, 8.1 Hz), 7.47(2H, d, J=8.1 Hz), 7.77(1H, dd, J=1.5, 8.1 Hz), 7.97(2H, d, J=8.1 Hz), 8.51(1H, dd, J=1.5, 5.1 Hz), 9.06(1H, t, J=5.9 Hz), 9.64(1H, s)

25

IR(KBr)cm $^{-1}$: 3261, 1642, 1523, 1310, 753

30

Example 16

N-(2-aminophenyl)-4-[N-(6-methylnicotinoyl)aminomethyl]benzamide (Table 1: Compound 143)

5

mp: 186-190°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.36(3H, s), 4.56(2H, d, J=5.9 Hz), 4.88(2H, s), 6.60(1H, dd, J=7.4, 7.8 Hz), 6.78(1H, d, J=7.8 Hz), 6.97(1H, dd, J=6.9, 6.9 Hz), 7.16(1H, d, J=7.4 Hz), 7.37(1H, d, J=8.3 Hz), 7.45(2H, d, J=8.3 Hz), 7.95(2H, d, J=8.3 Hz), 8.13(1H, dd, J=2.0, 8.3 Hz), 8.96(1H, s), 9.24(1H, t, J=5.9 Hz), 9.63(1H, br.s)

15

IR(KBr)cm⁻¹ : 3302, 1636, 1602, 1523, 1489, 1457, 1313, 751

Example 17

N-(2-aminophenyl)-4-[N-(2-chloronicotinoyl)aminomethyl]benzamide (Table 1: Compound 154)

20

mp: 176-178°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.54(2H, t, J=5.9 Hz), 4.90(2H, br.s), 6.60(1H, ddd, J=1.5, 7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, ddd, J=1.5, 7.3, 7.3 Hz), 7.18(1H, d, J=8.1 Hz), 7.48-7.54(3H, m), 7.94-7.99(3H, m), 8.49(1H, dd, J=2.1, 5.1 Hz), 9.23(1H, br.t, J=5.9 Hz), 9.65(1H, br.s)

25

IR(KBr)cm⁻¹ : 3264, 1649, 1524, 1400, 1309, 751

30

Example 18

N-(2-aminophenyl)-4-[N-(6-chloronicotinoyl)aminomethyl]benzamide (Table 1: Compound 156)

5

mp: 205-208°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 5.57(2H, d, J=5.9 Hz), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.45(2H, d, J=8.1 Hz), 7.66(1H, d, J=8.8 Hz), 7.95(2H, d, J=8.1 Hz), 8.27-8.32(1H, m), 8.90(1H, d, J=2.1 Hz), 9.38(1H, t, J=5.9 Hz), 9.63(1H, s)

IR(KBr)cm⁻¹ : 3318(br.), 2929, 1646, 1590, 1525, 1503, 1454, 1108, 745

15 Example 19

N-(2-aminophenyl)-4-(N-isonicotinoylaminomethyl)benzamide (Table 1: Compound 183)

20 mp: 234-237°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.57(2H, t, J=5.9 Hz), 4.88(2H, br.s), 6.59(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.45(2H, d, J=8.1 Hz), 7.81(2H, d, J=1.5, 4.4 Hz), 7.95(2H, d, J=8.1 Hz), 8.75(2H, d, J=6.6 Hz), 9.41(1H, t, J=5.9 Hz), 9.62(1H, br.s)

IR(KBr)cm⁻¹ : 3298, 1646, 1550, 1525, 1457, 1304, 843, 760, 695

30

Example 20

N-(2-aminophenyl)-4-[N-(pyrazin-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 191)

5

mp: 207°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.58(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.59(1H, dd, J=7.3, 7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.94(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.15(1H, d, J=7.3 Hz), 7.45(2H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 8.77(1H, d, J=1.5 Hz), 8.90(1H, d, J=2.1 Hz), 9.21(1H, s), 9.55-9.61(2H, m)

IR(KBr)cm⁻¹ : 3368(br.), 1657, 1524, 1455, 1295, 1023, 751

15 Example 21

N-(2-aminophenyl)-4-[N-(thiophen-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 201)

20 mp: 202-205°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.52(2H, t, J=5.9 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.15-7.18(2H, m), 7.43(2H, d, J=8.1 Hz), 7.78(1H, d, J=4.4), 7.82(1H, d, J=3.7 Hz), 7.95(2H, d, J=8.1 Hz), 9.12(1H, br.t, J=5.9 Hz), 9.62(1H, br.s)

IR(KBr)cm⁻¹ : 3306, 1633, 1523, 1456, 1297, 750, 716

30

Example 22

N-(2-aminophenyl)-4-[N-(furan-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 205)

5

mp: 197°C(dec.)

¹H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.59(2H, d, J=6.6 Hz), 4.86(2H, br.s), 6.59(1H, dd, J=6.6, 6.6 Hz), 6.63(1H, dd, J=1.5, 3.6 Hz), 6.78(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 6.6 Hz), 7.10-7.20(2H, m), 7.41(2H, d, J=8.1 Hz), 7.84(1H, s), 7.94(2H, d, J=8.1 Hz), 9.00(1H, br. t, J=5.9 Hz), 9.62(1H, s)

IR(KBr)cm⁻¹ : 3245, 1651, 1573, 1545, 1323, 1241, 745

15 Example 23

N-(2-aminophenyl)-4-[N-(pyrrol-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 209)

20 mp: 216-220°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.50(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.10(1H, dd, J=2.1, 5.9 Hz), 6.59(1H, dd, J=7.3, 7.3 Hz), 6.77(1H, dd, J=1.5, 8.1 Hz), 6.84-6.88(2H, m), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.41(2H, d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.62(1H, br.t, J=5.9 Hz), 9.62(1H, br.s)

IR(KBr)cm⁻¹ : 3275, 1655, 1584, 1534, 1458, 1316, 747

Example 24

N-(2-aminophenyl)-4-[N-(N'-methyl-1H-pyrrol-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 210)

5

mp: 177-179°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.84(3H, s), 4.46(2H, d, J=5.9 Hz), 4.88(2H, br.s), 6.03(1H, dd, J=2.1, 4.4 Hz), 6.59(1H, dd, J=8.1, 8.1 Hz),
10 6.77(1H, d, J=8.1 Hz), 6.84-6.97(2H, m), 7.16(1H, d, J=7.3 Hz), 7.41(2H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 8.61(1H, t, J=5.9 Hz), 9.62(1H, br.s)

IR(KBr)cm⁻¹ : 3325(br.), 1630, 1551, 1520, 1507, 1324, 1265, 1154, 740

15 Example 25

N-(2-aminophenyl)-4-[N-(isoxazol-5-yl)carbonylaminomethyl]benzamide (Table 1: Compound 212)

20 mp: 183-185°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.53(2H, d, J=6.6 Hz), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.12(1H, d, J=2.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.44(2H, d, J=8.1 Hz),
25 7.95(2H, d, J=8.1 Hz), 8.76(1H, d, J=1.5 Hz), 9.61(1H, t, J=5.9 Hz), 9.64(1H, br.s)

IR(KBr)cm⁻¹ : 3278(br.), 1636, 1576, 1522, 1458, 1220, 749

30

Example 26

N-(2-aminophenyl)-4-[N-(3-methylisothiazol-5-yl)carbonylaminomethyl]benzamide (Table 1: Compound 213)

5

mp: 168-169°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.47(3H, s), 4.54(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, ddd, J=1.0, 7.3, 8.1 Hz), 7.17(1H, d, J=7.3 Hz), 7.44 (2H, d, J=8.1 Hz), 7.73(1H, s), 7.96(2H, d, J=8.1 Hz), 9.44(1H, t, J=5.9 Hz), 9.64(1H, br.s)

10

IR(KBr)cm⁻¹ : 3310, 1637, 1503, 1294, 751

15 Example 27

N-(2-aminophenyl)-4-[N-(imidazol-4-yl)carbonylaminomethyl]benzamide (Table 1: Compound 214)

20 mp: (amorphous).

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.49(2H, d, J=6.4 Hz), 4.87(2H, br.s), 6.59(1H, dd, J=6.9, 6.9 Hz), 6.77(1H, d, J=6.9 Hz), 6.96(1H, dd, J=7.4, 7.4 Hz), 7.16(1H, d, J=6.9 Hz), 7.41(2H, d, J=6.9 Hz), 7.64(1H, br.s), 7.73(1H, br.s), 7.92(2H, d, J=6.9 Hz), 8.56(1H, br.t, J=6.4 Hz), 9.61(1H, s), 12.5(1H, br.s)

25

IR(KBr)cm⁻¹ : 3278(br.), 1636, 1576, 1522, 1458, 1220, 749

Example 28

N-(2-aminophenyl)-4-[N-(3-aminophenyl)acetylaminomethyl]benzamide (Table 1: Compound 23)

5

mp: 171-176°C

¹ H NMR(270 MHz, DMSO-d6) .delta. ppm: 4.34(2H, d, J=5.9 Hz), 5.24(4H, br.s), 6.48-6.63(4H,m), 6.78-6.81(1H, m), 6.94-7.00(2H, m), 7.18(1H, d, J=8.1 Hz), 7.34(2H, d, J=8.1 Hz), 7.92(2H, d, J=8.1 Hz), 8.50(1H, t, J=5.9 Hz), 9.61(1H, s)

10

Example 29

15 N-(2-aminophenyl)-4-[N-(pyridin-3-yl)acetylaminomethyl]benzamide (Table 1: Compound 74)

mp: 127°C

20 ¹ H NMR(270 MHz, DMSO-d6) .delta. ppm: 3.84(2H, s), 4.40(2H, d, J=5.8 Hz), 7.15-7.29(3H, m), 7.37(1H, d, J=6.6 Hz), 7.43(2H, d, J=8.8 Hz), 7.96(1H, m), 7.98(2H, d, J=8.8 Hz), 8.40(1H, d, J=8.8 Hz), 8.79-8.87(3H, m), 10.20(1H, s)

25

30

Example 30

N-(2-aminophenyl)-4-[N-[3-(pyridin-3-yl)propionyl]aminomethyl]benzamide
(Table 1: Compound 75)

5

mp: 183-186°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.51(2H, t, J=7.3 Hz), 2.88(2H, d, J=7.3 Hz), 4.31(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 8.1 Hz),
10 6.78(1H, d, J=8.1 Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.23(2H, d, J=8.8 Hz), 7.28-7.33(1H, m), 7.63(1H, d, J=8.1 Hz), 7.89(2H, d, J=8.1 Hz), 8.41-8.45(3H, m), 9.62(1H, br.s)

IR(KBr)cm⁻¹ : 3407, 3313, 1640, 1552, 1522, 1456, 1309, 746, 717

15

Example 31

N-(2-aminophenyl)-4-[N-[4-(pyridin-3-yl)-1,4-dioxobutyl]aminomethyl]benzamide
(Table 1: Compound 100)

20

mp: 145-147°C(dec.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.37-2.50(2H, m), 2.62-2.68(2H, m), 4.13(2H, s), 4.86(2H, s), 6.56-6.61(1H, m), 6.76-6.79(1H, m), 6.94-6.99(1H, m),
25 7.10-7.39(4H, m), 7.43-7.46(1H, m), 7.78(2H, d, J=8.1 Hz), 8.60-8.64(1H, m), 9.58(1H, s)

IR(KBr)cm⁻¹ : 3348, 1691, 1655, 1534, 1508, 1458, 1395, 1315, 1083, 746

30

Example 32

N-(2-aminophenyl)-4-[N-(5-chloropyridin-3-yl)oxyacetylaminomethyl]benzamide
(Table 1: Compound 158)

5

mp: 199-201°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.43(2H, d, J=6.6 Hz), 4.75(2H, s),
4.87(2H, br. s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd,
10 J=7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.37(2H, d, J=8.1 Hz), 7.59(1H, d, J=2.2
Hz), 7.93(2H, d, J=8.1 Hz), 8.25(1H, d, J=1.5 Hz), 8.81(1H, t, J=6.6 Hz),
9.64(1H, s)

IR(KBr)cm⁻¹ : 3288, 3058, 1675, 1633, 1523, 1457, 1314, 912, 755

15

Example 33

N-(2-amino-5-methoxyphenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzami
de (Table 1: Compound 175)

20

mp: 141-144°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.66(3H, s), 4.43(2H, d, J=5.9 Hz),
4.49(2H, br.s), 4.68(2H, s), 6.62(1H, dd, J=2.9, 8.8 Hz), 6.75(1H, d, J=8.8 Hz),
25 6.91(1H, d, J=2.2 Hz), 7.37(4H, m), 7.92(2H, d, J=8.8 Hz), 8.21(1H, dd, J=1.5,
4.4 Hz), 8.35(1H, d, J=2.7 Hz), 8.81(1H, s), 9.65(1H, s)

30

Example 34

N-(2-aminophenyl)-4-[N-[3-(pyridin-3-yl)-1,3-dioxopropyl]aminomethyl]benzamide (Table 1: Compound 98)

5

mp: 204-206°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.08(4/3H, s), 4.39(4/3H, d, J=5.9 Hz), 4.49(2/3H, d, J=5.9 Hz), 4.90(2H, br.s), 5.93(1/3H, s), 6.60(1H, t, J=7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, t, J=7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.3-7.7(3H, m), 7.8-8.4(3H, m), 8.6-9.2(3H, m), 9.64(1H, s), 14.74(1/3H, s). (2:1 equilibrium mixture)

IR(KBr)cm⁻¹ : 3282, 1690, 1645, 1527, 1421, 1314, 1217, 1028, 994, 911, 753, 701

Example 35

N-(2-aminophenyl)-4-[N-[N-(pyridin-3-yl)aminoacetyl]aminomethyl]benzamide (Table 1: Compound 96)

20

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.77(2H, d, J=6.6 Hz), 4.37(2H, d, J=5.9 Hz), 4.87(2H, br.s), 6.27(1H, t, J=5.9 Hz), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, 7.3 Hz), 6.87(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 8.1 Hz), 7.09(1H, d, J=4.4 Hz), 7.12(1H, d, J=4.4 Hz), 7.16(1H, d, J=8.1 Hz), 7.33(2H, d, J=8.8 Hz), 7.81(1H, d, J=4.4 Hz), 7.91(2H, d, J=7.3 Hz), 7.99(1H, d, J=2.9 Hz), 8.59(1H, br.t, J=5.1 Hz), 9.63(1H, br.s)

30

IR(KBr)cm⁻¹ : 3350, 1658, 1525, 1502, 1314, 750

Example 36

N-(2-aminophenyl)-4-[N-(2-aminothiazol-4-yl)acetylaminomethyl]benzamide
(Table 1: Compound 220)

5

mp: (amorphous).

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.34(2H, s), 4.35(2H, d, J=5.9 Hz),
4.87(2H, s), 6.25(1H, s), 6.59(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz),
10 6.87(2H, s), 6.96(1H, dd, J=7.3, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.37(2H, d,
J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 8.44(1H, t, J=5.9 Hz), 9.62(1H, s)

Example 37

15 N-(2-aminophenyl)-4-[N-(quinolin-6-yl)carbonylaminomethyl]benzamide (Table
1: Compound 231)

mp: 209-210°C

20 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.62(2H, d, J=5.9 Hz), 4.88(2H, s),
6.60(1H, t, J=7.7 Hz), 6.78(1H, d, J=7.3 Hz), 6.95(1H, d, J=7.3 Hz), 7.17(1H, d,
J=7.3 Hz), 7.49(2H, d, J=8.8 Hz), 7.62(1H, dd, J=4.4, 8.1 Hz), 7.96(2H, d, J=8.8
Hz), 8.10(1H, d, J=8.8 Hz), 8.23(1H, dd, J=2.2, 8.8 Hz), 8.38(1H, m), 8.49(1H,
d, J=8.1 Hz), 8.58(1H, s), 8.99(1H, s), 9.64(1H, s)

25

IR(KBr)cm⁻¹ : 3301, 1640, 1614, 1545, 1496, 1312, 910, 853, 745

30

Example 38

N-(2-aminophenyl)-4-[N-(furo[3,2-b]pyridin-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 233)

5

mp: 191°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.58(2H, d, J=5.9 Hz), 4.88(2H, s), 6.57-6.62(1H m), 6.76-6.79(1H, m), 6.93-6.99(1H, m), 7.15-7.25(1H, m), 7.45-10 7.52(3H, m), 7.74(1H, s), 7.95(2H, d, J=8.1 Hz), 8.13(1H, d, J=8.8 Hz), 8.63(1H, d, J=3.7 Hz), 9.54(1H, t, J=5.9 Hz), 9.64(1H, s)

IR(KBr)cm⁻¹ : 3406, 1662, 1529, 1507, 1420, 1313, 1209, 1139, 1170, 1139, 924, 741

15

Example 39

N-(2-aminophenyl)-4-[N-(furo[2,3-c]pyridin-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 234)

20

mp: 210°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.58(2H, J=6.6 Hz), 4.87(2H, s), 6.57-6.62(1H, m), 6.76-6.79(1H, m), 6.93-6.99(1H, m), 7.14-7.17(1H, m), 25 7.47(2H, d, J=8.1 Hz), 7.66(1H, s), 7.82(1H, d, J=4.4 Hz), 7.96(2H, d, J=8.1 Hz), 8.48(1H, d, J=5.1 Hz), 9.06(1H, s), 9.60-9.64(2H, m)

IR(KBr)cm⁻¹ : 3320, 1653, 1632, 1598, 1457, 1424, 1308, 1187, 1033, 853, 749

30

Example 40

N-(2-hydroxyphenyl)-4-[N-[3-(pyridin-3-yl)propionyl]aminomethyl]benzamide

5 (Table 1: Compound 125)

mp: (amorphous)

¹ H NMR(270 MHz, CD₃OD) .delta. ppm: 2.61(2H, t, J=7.3 Hz), 3.00(2H, t,
10 J=7.3 Hz), 4.39(2H, s), 7.04(1H, ddd, J=1.5, 8.1, 8.1 Hz), 7.25(2H, d, J=8.1 Hz),
7.33(1H, dd, J=5.1, 8.1 Hz), 7.69(1H, d, J=8.1 Hz), 7.85(2H, d, J=8.1 Hz),
7.86(1H, d, J=8.1 Hz), 8.41(2H, br.s)

IR(neat)cm⁻¹ : 3276, 1645, 1614, 1536, 1509, 1435, 1415, 1385, 1333, 1280,
15 1247, 1091, 737

Example 41

20 N-(2-hydroxyphenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide (Table
1: Compound 93)

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆): 4.43(2H, d, J=6.6 Hz), 4.69(2H, s), 6.83(1H, t,
25 J=6.6 Hz), 6.91(1H, d, J=8.1 Hz), 7.68(1H, d, J=6.6 Hz), 7.82(2H, d, J=8.1 Hz),
8.21(1H, d, J=4.4 Hz), 8.35(1H, d, J=2.2 Hz), 8.81(1H, t, J=6.6 Hz), 9.48(1H, s),
9.75(1H, s)

30 IR(KBr)cm⁻¹ : 3399, 1664, 1535, 1236, 1064

Example 42

N-(2-hydroxyphenyl)-4-[N-(pyridin-3-yl)acetylaminoethyl]benzamide (Table 1: Compound 117)

5

mp: 201-202°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.56(2H, s), 4.37(2H, d, J=5.9 Hz),
6.83(1H, ddd, J=1.5, 8.1, 8.1 Hz), 6.92(1H, br.d, J=8.1 Hz), 7.03(1H, ddd, J=1.5,
10 8.1, 8.1 Hz), 7.34(1H, dd, J=3.7, 8.1 Hz), 7.37(2H, d, J=8.1 Hz), 7.70(2H, d,
J=8.1 Hz), 7.91(2H, d, J=8.1 Hz), 8.45(1H, br.d, J=3.7 Hz), 8.49(1H, s),
8.73(1H, t, J=5.9 Hz), 9.47(1H, s), 9.73(1H, br.s)

IR(KBr)cm⁻¹ : 3272, 3067, 1661, 1647, 1598, 1536, 1455, 1334, 1288, 1194,
15 1024, 742

Example 43

20

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetyl-N-[3-(pyridin-3-yl)propyl]aminomethyl]benzamide (Table 1: Compound 91)

mp: (amorphous)

25

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.77-1.93(2H, m), 2.50-2.63(2H, m),
3.16-3.30(2H, m), 4.63(1.2H, s), 4.71(0.8H, s), 4.88(1.2H, s), 4.95(0.8H, s),
5.05(2H, s), 6.57-6.63(1H, m), 6.77-6.79(1H, m), 6.94-7.00(1H, m), 7.11-
7.42(5H, m), 7.58-7.64(1H, m), 7.92-8.02(2H, m), 8.15-8.43(5H, m), 9.65(0.6H,
30 s), 9.69(0.4H, s)(a mixture of rotational isomers)

Example 44

N-(2-aminophenyl)-4-[N-methyl-N-(pyridin-3-yl)oxyacetyl]aminomethylbenzamide (Table 1: Compound 92)

5

mp: 117-120°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.84 and 2.99(total 3H, s), 4.60 and 4.69(total 2H, s), 4.90(2H, br.s), 4.99 and 5.08(total 2H, s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.30-7.43(4H, m), 7.95 and 8.01(total 2H, d, J=8.1 Hz), 8.17(1H, d, J=4.4 Hz), 8.31(1H, d, J=2.9 Hz), 9.65 and 9.68(total 1H, br.s) (a mixture of rotational isomers)

15 IR(KBr)cm⁻¹ : 3298, 1665, 1501, 1425, 1310, 1276, 1254, 1078, 799, 746, 703

Example 45

20

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxamoylaminomethyl]benzamide (Table 1: Compound 95)

(45-1) Ethyl N-(pyridin-3-yl)oxamate (388 mg, 2 mmol) and 638 mg of the compound from the process (1-4) (2 mmol) were dissolved in ethanol, and the mixture was heated with stirring at 40 to 50°C for 2.5 hours. The precipitated crystals were collected by filtration and washed with 2 ml of ethanol and 3 ml of diethyl ether. The crystals were dried to give 724 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)oxamoylaminomethyl]benzamide (Yield: 74%).

30

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.44(9H, s), 4.49(2H, d, J=5.9 Hz),

7.10-7.30(2H, m), 7.35-7.57(5H, m), 7.93(2H, d, J=8.1 Hz), 8.21(1H, br.d, J=5.1 Hz), 8.35(1H, dd, J=1.5, 5.1 Hz), 8.68(1H, br.s), 9.00(1H, d, J=2.9 Hz), 9.70(1H, t, J=5.9 Hz), 9.82(1H, s), 10.98(1H, br.s)

- 5 (45-2) To a suspension of 720 mg of the compound from the process (45-1) in 8 ml of methanol was added 8 ml of 4N hydrochloric acid-dioxane solution. After stirring for 3 hours, the mixture was poured into a diluted sodium hydroxide aq. to be basified, and the precipitated crystals were collected by filtration. The crystals were recrystallized from THF/methanol=1:1, to give 280 mg of the
10 desired product.

mp: 254-258°C(dec.)

- ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.67(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.59(1H, dd, J=7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.38-7.44(1H, m), 7.43(2H, d, J=8.1 Hz), 7.95(2H, d, J=8.1 Hz), 8.18-8.24(1H, m), 8.34(1H, dd, J=1.5, 4.4 Hz), 9.00(1H, d, J=2.1 Hz), 9.63(1H, s), 9.69(1H, br.t, J=6.6 Hz), 10.97(1H, br.s)

- 20 IR(KBr.cm-1): 3312, 3270, 1663, 1636, 1521, 1312, 1296, 1019

Example 46

- Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide (Table 1: Compound 61)
25

- (46-1) To a suspension of 0.22 g of sodium hydride (60% oil dispersion, 5.5 mmol) in 2 ml of DMF was added dropwise a solution of 0.48 g of 3-hydroxypyridine (5.0 mmol) in 2 ml of DMF at room temperature, and the
30 mixture was stirred for an hour. The resulting brown solution was ice-cooled, 0.81 ml of tert-butyl bromoacetate (5.5 mmol) was added, and the mixture was stirred under ice-cooling for an hour followed by stirring at room temperature for

2 hours. After addition of water, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:ethyl acetate=5:1), to give 0.34 g of tert-butyl 3-pyridyloxyacetate
5 (Yield: 32.5%) as a clear oil.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.49(9H, s), 4.56(2H, s), 7.18-7.24(2H, m), 8.26(1H, dd, J=1.5, 3.6 Hz), 8.32(1H, d, J=2.9 Hz)

10 (46-2) To a solution of 0.14 g of the compound from the process (46-1) (0.67 mmol) in 2 ml of dichloromethane was added 2 ml of trifluoroacetic acid, and the solution was stirred at room temperature for 3 hours. After evaporation, diisopropyl ether was added, and the precipitated solid was collected by filtration and dried to give 0.15 g of 3-pyridyloxyacetic acid trifluoroacetate
15 (Yield: 83.8%) as a light yellow solid.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.86(2H, s), 7.57(1H, dd, J=4.4, 8.1 Hz), 7.67(1H, ddd, J=1.5, 1.5, 8.8 Hz), 8.31(1H, d, J=5.1 Hz), 8.46(1H, d, J=2.1 Hz), 13.00(1H, br.s)

20

(46-3) To a suspension of 100 mg of the compound from the process (46-2) (0.37 mmol) and 255 mg of the compound from Example 1, the process (1-4) (0.75 mmol) in 5 ml of dichloromethane was added 0.14 ml of triethylamine (1.0 mmol), and the mixture was cooled with ice. Under ice-cooling, to the mixture
25 was added a solution of 140 mg of 2-chloro-1,3-dimethylimidazolinium chloride (0.83 mmol) in 6 ml of dichloromethane, and the mixture was warmed to room temperature with stirring for 7 hours, and left at room temperature overnight. After adding water and saturated brine, the mixture was extracted with chloroform.

30

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl

acetate:methanol=10:1) to give 0.37 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide (Yield: quantitative) as a clear oil.

5 ¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.52(9H, s), 4.62(2H, s), 4.63(2H, d, J=7.3 Hz), 6.76(1H, br.s), 6.90-7.00(1H, br.s), 7.15-7.35(5H, m), 7.40(2H, d, J=8.1 Hz), 7.82(1H, d, J=8.1 Hz), 7.95(2H, d, J=8.1 Hz), 8.32(1H, dd, J=2.1, 4.4 Hz), 8.37(1H, d, J=2.8 Hz), 9.20(1H, br.s)

10 (46-4) To a solution of 175 mg of the compound from the process (46-3) (0.37 mmol) in 2 ml of dioxane and 2 ml of methanol was added 2 ml of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 2 hours. After adding saturated sodium bicarbonate aq., the mixture was
15 dried and evaporated. To the residue was added methanol and diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 90 mg of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide (Yield: 64.6%) as an opalescent solid.

20 mp: 154-155°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.42(2H, d, J=5.9 Hz), 4.69(2H, s), 4.89(2H, br.s), 6.59(1H, dd, :J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.33-7.39(4H, m), 7.92(2H, d, J=8.1 Hz),
25 8.21(1H, dd, J=1.5, 4.4 Hz), 8.35(1H, d, J=2.9 Hz), 8.80(1H, br.t, J=5.9 Hz), 9.63(1H, br.s)

IR(KBr)cm⁻¹ : 3307, 1672, 1631, 1523, 1456, 1429, 1269, 1231, 803, 756

Example 47

Preparation of N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)oxy]propionylaminomethyl]benzamide (Table 4: Compound 3)

5

(47-1) To a suspension of 1.20 g of sodium hydride (60% oil dispersion; 30.0 mmol) in 10 ml of dry DMF at room temperature were added dropwise 2.85 g of 3-hydroxypyridine (30 mmol) in 10 ml of dry DMF, maintaining the temperature below 40°C, and the mixture was stirred at room temperature for 90 min. Under ice-cooling, 6.28 g of tert-butyl 2-bromopropionate (30 mmol) in 10 ml of dry DMF were slowly added dropwise, maintaining the inner temperature within 5 to 10°C, and then the mixture was warmed to room temperature with stirring for 4 hours. After neutralizing with saturated sodium bicarbonate aq., the mixture was extracted with ethyl acetate. The organic layer was washed with water and then saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: n-hexane:ethyl acetate=2:1) to give 4.15 g of tert-butyl 2-(pyridin-3-yl)oxypropionate (Yield: 62%) as a brown oil.

15

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.44(9H, s), 1.61(3H, d, J=7.3 Hz), 4.66(1H, q, J=7.3 Hz), 7.13-7.23(2H, m), 8.24(1H, dd, J=1.5, 4.4 Hz), 8.29(1H, d, J=2.1 Hz)

20

(47-2) To a solution of 1.65 g of the compound from the process (47-1) (7.4 mmol) in 9 ml of dichloromethane was added 9 ml of trifluoroacetic acid, maintaining the temperature below 30°C, and then the mixture was stirred at room temperature for 8 hours. After evaporation, diisopropyl ether was added and the precipitated solid was collected by filtration and dried to give 1.86 g of 2-(pyridin-3-yl)oxypropionic acid trifluoroacetate (Yield 43.5%) as a light brown solid.

25

30

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.53(3H, d, J=6.6 Hz), 5.12(1H, q, J=6.6 Hz), 7.60-7.75(2H, m), 8.35(1H, d, J=5.1 Hz), 8.47(1H, s), 12.9(1H, br.s)

(47-3) To a suspension of 0.98 g of the compound from the process (47-2) (3.5 mmol) and 1.02 g of the compound from Example 1, the process (1-4) (3.0 mmol) in 20 ml of dichloromethane was added 1.3 ml of triethylamine (9.0 mmol) and then the mixture was ice-cooled. Under ice-cooling, 0.59 g of 2-chloro-1,3-dimethylimidazolidinium chloride (3.5 mmol) in 5 ml of dichloromethane was added dropwise, and the mixture was stirred for additional 2 hours. The mixture was neutralized with saturated sodium bicarbonate aq., and then extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:methanol=10:1) to give 1.64 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-[N-[2-(pyridin-3-yl)oxypropionyl]aminomethyl]benzamide as a mixture with 1,3-di-methyl-2-imidazolinone.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.51(9H, s), 1.64(3H, d, J=7.3 Hz), 4.54(2H,m), 4.78(1H, q, J=6.6 Hz), 6.87(2H, br.s), 7.13-7.30(6H, m), 7.81(1H, d, J=7.3 Hz), 7.90(2H, d, J=8.1 Hz), 8.29(1H, dd, J=1.5, 4.4 Hz), 8.33(1H, d, J=2.1 Hz), 9.22(1H, br.s)

(47-4) The compound from the process (47-3) (1.64 g) was dissolved in 10 ml of dioxane and 4 ml of methanol. To the solution was added 10 ml of 4N hydrochloric acid-dioxane solution at room temperature, and the mixture was stirred for 2 hours. The mixture was neutralized with saturated sodium bicarbonate aq. and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue were added methanol and diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 0.71 g of N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)oxy]propionylaminomethyl]benzamide (Yield: 60.5% for the 2 steps) as a white solid.

mp: 171-173°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.51(3H, d, J=6.6 Hz), 4.36(2H, d, J=5.9 Hz), 4.89(2H, br.s), 4.90(1H, t, J=6.6 Hz), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.15(1H, d, J=7.3 Hz), 7.27(2H, d, J=8.1 Hz), 7.33-7.37(2H, m), 7.89(2H, d, J=8.1 Hz), 8.21(1H, dd, J=2.9, 2.9 Hz), 8.32(1H, d, J=1.5 Hz), 8.82(1H, t, J=5.9 Hz), 9.63(1H, br.s)

Example 48

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 82)

(48-1) To a solution of 384 mg of 3-pyridinemethanol (3.52 mmol) in 5 ml of dry THF were added 523 mg of N,N'-carbonyldiimidazole (3.22 mmol) at room temperature. After stirring for an hour, to the mixture was added 1.0 g of the compound from Example 1, the process (1-4) (2.93 mmol) in 6 ml of dry THF.

After being left at room temperature overnight, to the mixture was added 100 ml of chloroform, and the mixture was washed with water (3.times.20 ml) and then saturated brine, and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (eluent: chloroform:methanol=30:1) to give 1.27 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Yield: quantitative) as an amorphous solid.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.51(9H, s), 4.45(2H, d, J=5.9 Hz), 5.16(1H, s), 7.10-7.50(7H, m), 7.70(1H, d, J=8.1 Hz), 7.80(1H, d, J=7.3 Hz), 7.93(1H, d, J=8.1 Hz), 8.57(1H, d, J=4.4 Hz), 8.63(1H, s), 9.17(1H, s).

(48-2) The compound from the process (48-1)(1.2 g, 2.8 mmol) was dissolved in 10 ml of methanol. To the solution was added 20 ml of 4N-hydrochloric acid-dioxane. The mixture was stirred at room temperature for 1.5 hours, and then poured into diluted sodium hydroxide aq. and extracted with chloroform

(3.times.60 ml). The combined organic layer was washed twice with saturated brine, dried over anhydrous magnesium sulfate and concentrated to give 0.88 g of crystals, which were then recrystallized from 16 ml of ethanol, to give 668 mg of N-(2-aminophenyl)-4-[N-(pyridin-3-

5 yl)methoxycarbonylaminomethyl]benzamide (Yield: 73%).

mp: 159-160°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.28(2H, d, J=5.9 Hz), 4.86(2H, s),
10 5.10(2H, s), 6.60(1H, t, J=7.3 Hz), 6.78(1H, d, J=7 Hz), 6.97(1H, t, J=7 Hz),
7.17(1H, d, J=8 Hz), 7.30-7.50(3H, m), 7.78(1H, d, J=8 Hz), 7.93(2H, d, J=8
Hz), 8.53(1H, d, J=3.7 Hz), 8.59(1H, s), 9.61(1H, s).

IR(KBr)cm⁻¹ : 3295, 1648, 1541, 1508, 1457, 1309, 1183, 742

15

As described in Example 48, the compounds of Examples 49 to 87 were prepared, each of whose melting point (mp), ¹ H NMR data and/or IR data are shown below.

20

Example 49

N-(2-aminophenyl)-4-[N-(benzyloxycarbonyl)aminomethyl]benzamide (Table 1:
Compound 11)

25

mp: 174-178°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.28(2H, d, J=5.9 Hz), 4.89(2H,
br.s), 5.06(2H, s), 6.59(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H,
30 dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.30-7.40(6H, m), 7.93(3H, m),
9.63(1H, s).

IR(KBr)cm⁻¹ : 3332, 1687, 1652, 1536, 1456, 1279, 747

Example 50

- 5 N-(2-aminophenyl)-4-[N-(4-(imidazol-1-yl)benzyl)oxycarbonylaminomethyl]benzamide (Table 1: Compound 47)

mp: 195-198°C

- 10 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.29(2H, d, J=6.6 Hz), 4.88(2H, s), 5.10(2H, s), 6.60-6.63(1H,m), 6.78(1H, d, J=8.1 Hz), 6.97(1H, t, J=7.3 Hz), 7.11(1H, s), 7.16(1H, d, J=7.3 Hz), 7.37(2H, d, J=8.1 Hz), 7.49(2H, d, J=8.8 Hz), 7.66(2H, d, J=8.1 Hz), 7.74(1H, s), 7.92-7.96(3H, m), 8.25(1H, s), 9.62(1H, s)

15

Example 51

- 20 N-(2-aminophenyl)-4-[N-(pyridin-2-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 171)

mp: 166-167°C

- 25 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.30(2H, d, J=5.9 Hz), 4.88(2H, br.s), 5.12(2H, s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.33(1H, dd, J=3.7, 7.3 Hz), 7.40(3H, d, J=8.1 Hz), 7.83(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.03(1H, t, J=5.9 Hz), 8.55(1H, d, J=5.1 Hz), 9.62(1H, br.s)

- 30 IR(KBr)cm⁻¹ : 3334, 1694, 1632, 1580, 1276, 755

Example 52

N-(2-aminophenyl)-4-[N-[2-(pyridin-2-yl)ethoxycarbonyl]aminomethyl]benzamide (Table 1: Compound 172)

5

mp: 146-148°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.04(2H, t, J=6.6 Hz), 4.23(2H, d, J=5.9 Hz), 4.36(2H, t, J=6.6 Hz), 4.88(2H, br.s), 6.60(1H, dd, J=7.3, 8.1 Hz),
10 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.15-7.30(3H, m), 7.34(2H, d, J=8.1 Hz), 7.69-7.77(2H, m), 7.92(2H, d, J=7.3 Hz), 8.50(1H, d, J=4.4 Hz), 9.62(1H, br.s)

15

IR(KBr)cm⁻¹ : 3330, 1690, 1633, 1594, 1524, 1277, 760

Example 53

20 N-(2-aminophenyl)-4-[N-(6-methylpyridin-2-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 179)

mp: 138°C

25 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.47(3H, s), 4.30(2H, d, J=5.9 Hz), 5.07(4H, s), 6.63(1H, t, J=8.1 Hz), 6.80(1H, d, J=7.34), 6.98(1H, t, J=8.1 Hz), 7.18(3H, d, J=7.3 Hz), 7.40(2H, d, J=8.1 Hz), 7.71(1H, t, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.03(1H, t, J=5.9 Hz), 9.66(1H, s)

30 IR(KBr)cm⁻¹ : 3335, 1693, 1634, 1259

Example 54

N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)ethoxycarbonyl]aminomethyl]benzamide (Table 1: Compound 83)

5

mp: 120-125°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.91(2H, t, J=6.6 Hz), 4.22(4H, t, J=6.6 Hz), 4.89(2H, s), 6.55-6.63(1H, m), 6.78(1H, dd, J=8.1, 1.5 Hz), 6.97(1H, t, J=6.6 Hz), 7.17(1H, d, J=6.6 Hz), 7.33(3H, d, J=8.1 Hz), 7.69(1H, d, J=8.1 Hz), 7.79(1H, t, J=6.6 Hz), 7.93(2H, d, J=8.0 Hz), 8.43-8.49(2H, m), 9.62(1H, s)

10

IR(KBr)cm⁻¹ : 3234, 1705, 1655, 1260

15

Example 55

N-(2-aminophenyl)-4-[N-[3-(pyridin-3-yl)propyloxycarbonyl]aminomethyl]benzamide (Table 1: Compound 84)

20

mp: 121-124°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.83-1.94(2H, m), 2.67(2H, t, J=7.3 Hz), 3.98(2H, t, J=6.6 Hz), 4.26(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.60(1H, dd, J=8.1, 8.1 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.29-7.33(1H, m), 7.37(1H, d, J=8.1 Hz), 7.64(1H, d, J=8.1 Hz), 7.81(1H, dd, J=5.9, 6.6 Hz), 7.94(2H, d, J=8.1 Hz), 8.40-8.44(2H, m), 9.63(1H, br.s)

25

30

IR(KBr)cm⁻¹ : 3348, 1696, 1635, 1523, 1458, 1302, 1272, 1141, 1019, 754, 713

Example 56

N-(2-aminophenyl)-4-[N-(2-methylpyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 142)

5

mp: 164-165°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.49(3H, s), 4.28(2H,d, J=6.6 Hz), 4.89(2H, s), 5.10(2H, s), 6.60(1H, t, J=6.6 Hz), 6.78(1H, d, J=8.1 Hz), 6.90(1H, t, J=7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.21-7.26(1H, m), 7.37(2H, d, J=8.1 Hz), 7.68(1H, d, J=6.6 Hz), 7.92-8.00(3H, m), 8.39(1H, d, J=4.4 Hz), 9.62(1H, s)

IR(KBr)cm⁻¹ : 3332, 1719, 1630, 1260

15

Example 57

N-(2-aminophenyl)-4-[N-(6-methylpyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 144)

20

mp: 164-165°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.46(3H, s), 4.27(2H, d, J=6.6 Hz), 4.88(2H, s), 5.05(2H, s), 6.59(1H, dt, J=1.5, 8.1 Hz), 6.78(1H, dd, J=1.5, 8.1 Hz), 6.97(1H, dt, J=1.5, 7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.26(1H, d, J=8.1 Hz), 7.36(2H, d, J=8.1 Hz), 7.67(1H, dd, J=2.2, 8.1 Hz), 7.93(3H, d, J=8.1 Hz), 8.45(1H, d, J=1.5 Hz), 9.62(1H, s)

IR(KBr)cm⁻¹ : 3293, 1701, 1632, 1260

30

Example 58

N-(2-aminophenyl)-4-[N-(2-chloropyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 155)

5

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.30(2H, d, J=5.9 Hz), 5.00(2H, s), 5.13(2H, s), 6.61(1H, t, J=7.3 Hz), 6.79(1H, dd, J=1.5, 8.1 Hz), 6.98(1H, dt, J=1.5, 7.3 Hz), 7.17(1H, d, J=6.6 Hz), 7.39(2H, d, J=8.8 Hz), 7.47-7.52(1H, m), 7.91-7.96(3H, m), 8.08(1H, t, J=5.9 Hz), 8.40(1H, dd, J=4.4, 1.5 Hz), 9.64(1H, s)

10

IR(KBr)cm⁻¹ : 3340, 1702, 1632, 1273

15

Example 59

N-(2-aminophenyl)-4-[N-(6-chloropyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 157)

20

mp: 180-185°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.24(2H, d, J=5.9 Hz), 4.89(2H, br.s), 5.10(2H, s), 6.60(1H, t, J=7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dt, J=1.5, 8.1 Hz), 7.16(1H, d, J=6.6 Hz), 7.37(2H, d, J=8.1 Hz), 7.56(1H, d, J=8.1 Hz), 7.85-8.02(4H, m), 8.44(1H, d, J=2.2 Hz), 9.62(1H, s)

25

IR(KBr)cm⁻¹ : 3346, 3282, 1696, 1533, 1271

30

Example 60

N-(2-aminophenyl)-4-[N-(pyridin-4-yl)methoxycarbonylaminomethyl]benzamide
(Table 1: Compound 181)

5

mp: 180-183°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.30(2H, d, J=6.6 Hz), 4.89 (2H, s),
5.12(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, dd, J=1.5, 7.3 Hz), 6.97(1H,
10 ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.34(2H, d, J=5.9 Hz), 7.39(2H,
d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.09(1H, t, J=5.9 Hz), 8.57(1H, d), 9.64(1H,
br.s)

IR(KBr)cm⁻¹ : 3394, 3290, 1711, 1645, 1624, 1535, 1504, 1321, 1251, 1138,
15 1049, 763

Example 61

20

N-(2-aminophenyl)-4-[N-[2-(thiophen-3-yl)ethoxycarbonyl]aminomethyl]benzami
de (Table 1: Compound 203)

mp: (amorphous)

25

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.90(2H, t, J=7.3 Hz), 4.17-4.26(4H,
m), 4.89(2H, s), 6.60(1H, t, J=8.1 Hz), 6.78(1H, d, J=6.6 Hz), 6.97(1H, t, J=7.3
Hz), 7.06(1H, d, J=5.1 Hz), 7.17(1H, d, J=7.3 Hz), 7.26(1H, s), 7.36(2H, d,
J=8.1 Hz), 7.47(1H, t, J=2.2 Hz), 7.81(1H, t, J=5.9 Hz), 7.93(2H, d, J=8.1 Hz),
30 9.63(1H, s).

IR(KBr)cm⁻¹ : 3314, 1716, 1638, 1252

Example 62

5 N-(2-aminophenyl)-4-[N-(3-phenyloxazol-5-yl)methoxycarbonylaminomethyl]benz amide (Table 1: Compound 211)

mp: 192-195°C

10 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.30(2H, d, J=5.9 Hz), 4.89(2H, s), 5.25(2H, s), 6.60(1H, t, J=6.6 Hz), 6.68(1H, d, J=8.1 Hz), 6.94(1H, t, J=7.3 Hz), 7.09(1H, s), 7.16(1H, d, J=7.3 Hz), 7.39(2H, d, J=8.1 Hz), 7.51(4H, d, J=2.2 Hz), 7.87-7.96(5H, m), 8.12(1H, t, J=5.9 Hz), 9.63(1H, s)

15 IR(KBr)cm⁻¹ : 3292, 1718, 1630, 1262

Example 63

20

N-(2-aminophenyl)-4-[N-(thiazol-5-yl)methoxycarbonylaminomethyl]benzamide
(Table 1: Compound 216)

mp: 168-175°C

25

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.28(2H, d, J=5.9 Hz), 4.91(2H, br.s), 5.30(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.36(2H, d, J=8.1 Hz), 7.91-8.00(4H, m), 9.09(1H, s), 9.63(1H, s)

30

IR(KBr)cm⁻¹ : 3346(br.), 1697, 1636, 1525, 1456, 1271, 873, 753

Example 64

N-(2-aminophenyl)-4-[N-[2-(4-methylthiazol-5-yl)ethoxycarbonyl]aminomethyl]benzamide (Table 1: Compound 217)

5

mp: 130-133°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.32(3H, s), 3.07(2H, t, J=5.9 Hz), 4.15(2H, t, J=5.9 Hz), 4.25(2H, d, J=6.6 Hz), 4.89(2H, s), 6.60(1H, t, J=5.9 Hz), 6.78(1H, dd, J=7.3, 1.5 Hz), 6.97(1H, dt, J=1.5, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.35(2H, d, J=8.1 Hz), 7.83(1H, t, J=5.9 Hz), 7.94(2H, d, J=8.1 Hz), 8.85(1H, s), 9.62(1H, s)

10

IR(KBr)cm⁻¹ : 3350, 1691, 1635, 1270

15

Example 65

20

N-(2-aminophenyl)-4-[N-(1-methylpiperidin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 225)

mp: 130-135°C

25

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.49-1.78(3H, m), 1.83-2.01(3H, m), 2.30(3H, s), 2.85(2H, t), 3.74-3.94(2H, m), 4.25(2H, d, J=5.8 Hz), 6.55-6.62(3H, m), 6.78(1H, d, J=8.1 Hz), 6.97(1H, t, J=7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.37(2H, d, J=8.1 Hz), 7.79(1H, t, J=6.6 Hz), 7.93(2H, d, J=8.0 Hz), 9.66(1H, s)

30

IR(KBr)cm⁻¹ : 3323, 2722, 1702, 1648, 1263

Example 66

N-(2-aminophenyl)-4-[N-(4-methylpiperazin-1-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 227)

5

mp: (amorphous)

^1H NMR(270 MHz, DMSO- d_6) δ , ppm: 1.73(2H, t, J=6.6 Hz), 2.36-2.63(13H, m), 4.00(2H, t, J=6.6 Hz), 4.30(2H, d, J=5.8 Hz), 6.55-6.63(4H, m),
10 6.78(1H, d, J=6.6 Hz), 6.97(1H, t, J=7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.37(2H, d, J=8.7 Hz), 7.73(1H, t, J=5.9 Hz), 7.94(2H, d, J=8.0 Hz), 9.66(1H, s)

IR(KBr)cm $^{-1}$: 3341, 2706, 1701, 1262

15

Example 67

20

N-(2-aminophenyl)-4-[N-(tetrahydrofuran-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 221)

mp: (amorphous)

25

^1H NMR(270 MHz, DMSO- d_6) δ , ppm: 1.50-1.60(1H, m), 1.88-2.00(1H, m), 2.44-2.54(1H, m), 3.41-3.47(1H, m), 3.56-3.77(3H, m), 3.85-4.04(2H, m),
4.25(2H, d, J=5.9 Hz), 4.89(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.17(1H, d, J=8.1 Hz), 7.37(2H, d, J=8.1
30 Hz), 7.81(1H, t, J=5.9 Hz), 7.94(2H, d, J=8.1 Hz), 9.62(1H, br.s)

IR(KBr)cm $^{-1}$: 3349, 1695, 1635, 1523, 1457, 1259, 754

Example 68

N-(2-aminophenyl)-4-[N-(phenoxy carbonyl)aminomethyl]benzamide (Table 1:

5 Compound 12)

mp: 174-175°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.36(2H, d, J=5.9 Hz), 4.90(2H,
10 br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.77(1H, dd, J=7.3, 7.3 Hz), 6.98(1H, ddd,
J=1.5, 7.3, 7.3 Hz), 7.05-7.24(4H, m), 7.39-7.46(4H, m), 7.97(2H, d, J=8.1 Hz),
8.41(1H, t, J=5.9 Hz), 9.65(1H, br.s)

IR(KBr)cm⁻¹ : 3443, 3362, 3313, 1732, 1706, 1636, 1527, 1493, 1458, 1305,
15 1217, 748

Example 69

20

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxycarbonylaminomethyl]benzamide
(Table 1: Compound 81)

mp: 209°C(dec.)

25

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.38(2H, d, J=6.6 Hz), 4.90(2H,
br.s), 6.55-6.63(1H, m), 6.78(1H, d, J=8.1 Hz), 7.00(1H, dd, J=7.3, 7.3 Hz),
7.17(1H, d, J=8.8 Hz), 7.37-7.47(3H, m), 7.64(1H, d, J=8.8 Hz), 7.97(2H, d,
J=8.1 Hz), 8.43(2H, d, J=3.1 Hz), 8.59(1H, t, J=5.9 Hz), 9.66(1H, br.s)

30

Example 70

N-(2-amino-5-fluorophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 110)

5

mp: 160-162°C

¹H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.28(2H, d, J=6.6 Hz), 4.81(2H, s),
5.10(2H, s), 6.70-6.90(2H, m), 7.10-8.00(8H, m), 8.53(1H, d, J=3.6 Hz),
10 8.59(1H, s), 9.61(1H, s)

IR(KBr)cm⁻¹ : 3269, 1716, 1638, 1488, 1436, 1247, 1141, 1043, 744

15

Example 71

N-(2-aminophenyl)-4-[N-(2-aminophenyl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 51)

20

mp: 149-151°C(dec.)

¹H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.28(2H, d, J=5.9 Hz), 4.88(2H, s),
4.96(2H, s), 5.06(2H, s), 6.53(1H, dd, J=7.3, 7.3 Hz), 6.56-6.67(2H, m),
25 6.78(1H, dd, J=1.5, 8.1 Hz), 6.93-7.12(3H, m), 7.16(1H, d, J=6.6 Hz), 7.38(2H,
d, J=8.1 Hz), 7.86(1H, t-like, J=5.9 Hz), 7.93(2H, d, J=8.1 Hz), 9.61(1H, s)

IR(KBr)cm⁻¹ : 3336, 1685, 1632, 1527, 1276, 748

30

Example 72

N-(2-aminophenyl)-4-[N-(quinuclidin-3-yl)oxycarbonylaminomethyl]benzamide

5 (Table 1: Compound 228)

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.30-1.90(4H, m), 1.90(1H, br.s),
10 2.45-2.80(6H, m), 3.04-3.13(1H, m), 4.15(2H, d, J=5.9 Hz), 4.55-4.60(1H, m),
4.88(2H, br.s), 6.60(1H, ddd, J=1.5, 7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz),
6.97(1H, ddd, J=1.5, 7.3, 7.3 Hz), 7.17(1H, d, J=6.6 Hz), 7.37(2H, d, J=8.1 Hz),
7.78(1H, t, J=5.9 Hz), 7.94(1H, d, J=7.3 Hz), 9.62(1H, s)

15 IR(KBr)cm⁻¹ : 3328, 2942, 1700, 1648, 1504, 1259, 749

Example 73

20

N-(2-aminophenyl)-4-[N-(3-aminophenyl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 52)

mp: 149-153°C(dec.)

25

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.27(2H, d, J=5.9 Hz), 4.88 and
4.89(total 4H, each br.s), 5.08(2H, s), 6.47-6.63(3H, m), 6.78(1H, d, J=8.1 Hz),
6.94-7.02(2H, m), 7.15(1H, dd, J=7.3, 8.8 Hz), 7.37(2H, d, J=8.1 Hz), 7.84(1H,
t, J=5.9 Hz), 7.93(2H, d, J=8.8 Hz), 9.61(1H, br.s)

30

IR.(KBr)cm⁻¹ : 3367, 1682, 1632, 1523, 1457, 1261, 754

Example 74

N-(2-aminophenyl)-4-[N-(1-methylimidazol-5-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 218)

5

mp: 162-165°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.62(3H, s), 4.27(2H, d, J=5.9 Hz), 4.91(2H, br.s), 5.05(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz),
10 6.95-7.00(2H, m), 7.16(1H, d, J=7.3 Hz), 7.36(2H, d, J=8.1 Hz), 7.63(1H, s), 7.87-7.95(3H, m), 9.64(1H, br.s)

IR(KBr)cm⁻¹ : 3293, 1688, 1651, 1534, 1506, 1259, 1121, 1043, 748

15

Example 75

N-(2-amino-4-chlorophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 113)

20

mp: 167-170°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.28(2H, d, J=5.9 Hz), 5.10(2H, s), 5.21(2H, s), 6.72(1H, dd, J=2.2, 8.1 Hz), 6.81(1H, d, J=2.2 Hz), 7.16(1H, d, J=8.1 Hz), 7.37(2H, d, J=8.1 Hz), 7.78(1H, d, J=8.1 Hz), 7.92(2H, d, J=8.1 Hz),
25 8.53(1H, d, J=4.4 Hz), 8.59(1H, s), 9.60(1H, s)

IR(KBr)cm⁻¹ : 3347, 3062, 2931, 1653, 1576, 1505, 1456, 1428, 1301, 1232, 1114, 1070, 1019

30

Example 76

N-(2-aminophenyl)-4-[N-(5-methoxypyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 161)

5

mp: 169-170°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.83(3H, s), 4.29(2H, d, J=6.6 Hz), 4.87(2H, s), 5.09(2H, s), 6.57-6.62(1H, m), 6.76-6.79(1H, m), 6.94-6.99(1H, m),
10 7.14-7.18(1H, m), 7.36-7.39(3H, m), 7.91-7.99(3H, m), 8.19-8.30(2H, m), 9.63(1H, s)

IR(KBr)cm⁻¹ : 3330, 1694, 1633, 1524, 1457, 1298, 1269, 1045, 760

15

Example 77

N-(2-aminophenyl)-4-[N-(pyrazin-2-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 192)

20

mp: 182°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.30(2H, d, J=6.6 Hz), 4.88(2H, br.s), 5.20(2H, s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.39(2H, d, J=8.8 Hz), 7.94(2H, d, J=8.8 Hz), 8.08(1H, t-like, J=6.6 Hz), 8.61(1H, s), 8.65(1H, s), 8.68(1H, s),
25 9.63(1H, s)

IR(KBr)cm⁻¹ : 3266, 1709, 1632, 1535, 1508, 1284, 1055, 1022, 744

30

Example 78

N-(2-amino-5-methoxyphenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 121)

5

mp: 141-143°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.66(3H, s), 4.29(2H, d, J=5.9 Hz), 4.51(2H, br.s), 5.10(2H, s), 6.63(1H, dd, J=2.9, 8.8 Hz), 6.74(1H, d, J=8.8 Hz),
10 6.91(1H, d, J=2.2 Hz), 7.38(2H, d, J=8.8 Hz), 7.41(1H, s), 7.79(1H, d, J=8.1 Hz), 7.92(2H, d, J=8.1 Hz), 7.98(1H, t, J=5.9 Hz), 8.54(1H, d, J=3.7 Hz), 8.60(1H, s), 9.65(1H, s)

15 Example 79

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methyl-N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 109)

20 mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.50(2H, s), 4.56(2H, s), 4.87(2H, s), 5.21(2H, s), 6.60(1H, t, J=7.7 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, d, J=7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.20-7.50(4H, m), 7.60-8.00(4H, m), 8.40-8.60(4H, m),
25 9.65(1H, s)

IR(KBr)cm⁻¹ : 3268, 1700, 1504, 1246, 1120, 940, 714

30

Example 80

N-(2-aminophenyl)-4-[N-[3-(pyridin-3-yl)propyl]-N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 120)

5

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.75-1.90(2H, m), 2.48-2.62(2H, m), 3.20-3.36(2H, m), 4.55(2H, s), 4.89(2H, s), 5.16(2H, s), 6.57-6.63(1H, m), 6.76-
10 6.80 (1H, m), 6.94-6.99(1H, m), 7.14-7.17(1H, m), 7.32-7.74(6H, m), 7.94(2H, d, J=8.1 Hz), 8.30-8.65(4H, m), 9.64(1H, s)

Example 81

15

N-(2-hydroxyphenyl)-4-[N-(pyridin-3-yl)methyl-N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 115)

mp: (amorphous)

20

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.52(2H, s), 4.57(2H, s), 5.20(2H, s), 6.84(1H, t, J=6.6 Hz), 6.93(1H, d, J=6.6 Hz), 7.03(1H, d, J=7.3 Hz), 7.37(4H, m), 7.68(2H, dd, J=1.5, 8.1 Hz), 7.92(2H, br.s), 8.53(4H, m), 9.49(1H, s),
25 9.77(1H, br.s)

25

IR(KBr)cm⁻¹ : 3035, 1698, 1243, 1118, 754, 640

30

Example 82

N-(2-hydroxyphenyl)-4-[N-(pyridin-3-yl)
methoxycarbonylaminomethyl]benzamide (Table 1: Compound 111)

5

mp: 162-164°C

¹H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.29(1H, d, J=5.9 Hz), 5.10(2H, s),
6.83(1H, t, J=8.1 Hz), 6.92(1H, d, J=6.6 Hz), 7.07(1H, t, J=6.6 Hz), 7.39(2H, d,
10 J=8.8 Hz), 7.43(1H, d, J=5.1 Hz), 7.68(2H, d, J=8.1 Hz), 7.80(1H, d, J=8.1 Hz),
7.92(2H, d, J=8.1 Hz), 7.99(1H, t, J=5.9 Hz), 8.54(1H, d, J=4.4 Hz), 8.60(1H, s),
9.49(1H, s), 9.76(1H, br.s)

15

IR(KBr)cm⁻¹ : 3333, 3259, 1694, 1645, 1529, 1267, 720

Example 83

N-(2,4-dihydroxyphenyl)-4-[N-(pyridin-3-yl)
20 methoxycarbonylaminomethyl]benzamide (Table 1: Compound 116)

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.27(2H, d, J=6.6 Hz), 5.10(2H, s),
25 6.20(2H, dd, J=2.2, 8.1 Hz), 6.39(2H, d, J=2.9 Hz), 6.88(2H, d, J=8.8 Hz),
7.33(1H, d, J=8.1 Hz), 7.41(1H, dd, J=5.1, 7.1 Hz), 7.89(1H, d, J=8.8 Hz),
7.98(1H, t, J=6.6 Hz), 8.05(2H, s), 8.52(1H, m), 8.59(1H, s), 9.30(2H, br.s)

30

IR(KBr)cm⁻¹ : 3387, 1702, 1612, 1311, 1169, 845

Example 84

N-(2-hydroxy-5-methylphenyl)-4-[N-(pyridin-3-yl)
methoxycarbonylaminomethyl]benzamide (Table 1: Compound 118)

5

mp: 155-155.5°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.22(3H, s), 4.29(2H, d, J=5.8 Hz),
5.11(2H, s), 6.82(2H, m), 7.39(2H, d, J=8.8 Hz), 7.42(2H, m), 7.51(1H, s),
10 7.79(1H, d, J=8.1 Hz), 7.92(1H, d, J=8.1 Hz), 7.98(1H, t, J=5.9 Hz), 8.54(1H, d,
J=4.4 Hz), 8.60(1H, s), 9.48(2H, d, J=8.1 Hz)

IR(KBr)cm⁻¹ : 3306, 1723, 1655, 1525, 801, 639

15

Example 85

N-(2-hydroxy-5-methoxyphenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl
]benzamide (Table 1: Compound 119)

20

mp: 175-176°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.69(3H, s), 4.29(2H, d, J=5.9 Hz),
5.10(2H, s), 6.63(1H, dd, J=2.9, 8.7 Hz), 6.84(1H, d, J=8.8 Hz), 7.41(4H, m),
25 7.79(1H, d, J=8.1 Hz), 7.91(1H, d, J=8.1 Hz), 7.99(1H, t, J=5.9 Hz), 8.54(1H, d,
J=5.1 Hz), 8.60(1H, s), 9.31(1H, s), 9.45(1H, s)

IR(KBr)cm⁻¹ : 3305, 1687, 1573, 1262, 1039, 868

30

Example 86

N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)ethoxycarbonyl]amino]benzamide
(Table 1: Compound 124)

5

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.00(2H, t, J=6.6 Hz), 4.37(2H, t, J=6.6 Hz), 4.87(2H, br.s), 6.60(1H, t, J=7.3 Hz), 6.97(1H, t, J=7.3 Hz), 7.15(1H, d, J=7.3 Hz), 7.36(1H, dd, J=4.4, 8.1 Hz), 7.56(2H, d, J=8.8 Hz), 7.92(2H, d, J=8.8 Hz), 8.46(1H, d, J=4.4 Hz), 8.54(1H, d, J=2.2 Hz), 9.95(1H, s)

10

IR(KBr)cm⁻¹ : 3285, 1695, 1519, 1315, 1233, 1079

15

Example 87

N-(2-aminophenyl)-5-[(pyridin-3-yl)methoxycarbonyl]aminobenzofuran-2-carboxamide (Table 3: Compound 2)

20

mp: 173-174°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 5.22(2H, s), 6.60(1H, dd, J=8.1, 8 Hz), 6.79(1H, dd, J=1.5, 8.1 Hz), 7.00(1H, dd, J=8.1, 8 Hz), 7.20(1H, dd, J=1.5, 8.1 Hz), 7.44(1H, m), 7.48(1H, dd, J=1.5, 8.8 Hz), 7.61(1H, d, J=8.8 Hz), 7.67(1H, s), 7.88(1H, dd, J=1.5, 8 Hz), 7.96(1H, d, J=1.5 Hz), 8.56(1H, dd, J=1.5, 4.8 Hz), 8.68(1H, d, J=1.5 Hz), 9.83(1H, s), 9.91(1H, s)

25

IR(KBr)cm⁻¹ : 3308, 1707, 1667, 1584, 1536, 1452, 1316, 1248, 1157, 1128, 1070, 955, 879, 795, 748, 710

30

Example 88

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxythiocarbonylaminoethyl]benzamide (Table 1: Compound 86)

5

(88-1) To a solution of 20 mg of 3-pyridinemethanol (0.18 mmol) in 5 ml of dry THF were added 30 mg of N,N'-thiocarbonyldiimidazole (0.16 mmol) at room temperature. After stirring overnight, to the mixture were added 50 mg of the compound from Example 1, the process (1-4) (0.14 mmol).

10

After leaving at room temperature overnight, to the solution was added 100 ml of chloroform, and the solution was washed with water (3.times.20 ml) and then saturated brine, and dried over anhydrous magnesium sulfate. After evaporation, the residue was purified by column chromatography on silica gel(eluent:chloroform:methanol=30:1) to give 70 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)methoxythiocarbonylaminoethyl]benzamide (Yield: 88%) as amorphous.

15

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.45(9H, s), 4.73(2H, d, J=5.9 Hz), 5.52(2H, s), 6.73-7.33(3H, m), 7.35-7.43(2H, m), 7.58-7.95(5H, m), 8.14-8.65(3H, m), 9.80(1H, s), 9.91(1H, t)

20

(88-2) To a solution of 50 mg of the compound from the process (88-1) (0.10 mmol) in 3 ml of methanol was added 3 ml of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 1.5 hours. The mixture was poured into diluted sodium hydroxide aq. to neutralize the residual hydrochloric acid, and then was extracted with chloroform (3.times.10 ml). The organic layer was washed twice with saturated brine, dried over anhydrous magnesium sulfate and concentrated to give 34 mg of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxythiocarbonylaminoethyl]benzamide (Yield: 87%)

25

30

mp: 154-156°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.73(2H, d, J=5.9 Hz), 4.88(2H, s),
5.52(2H, s), 6.60(1H, t, J=7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.96(1H, t, J=8.1 Hz),
7.16(1H, d, J=7.3 Hz), 7.29-7.41(3H, m), 7.83-7.95(3H, m), 8.50-8.56(1H, m),
5 8.65(1H, s), 9.62(1H, s), 9.93(1H, s)

IR(KBr)cm⁻¹ : 3204, 3035, 1631, 1523, 1456, 1289, 1191, 920, 753

10 Example 89

Preparation of N-(2-aminophenyl)-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (Table 1: Compound 88)

15 (89-1) To a solution of 0.28 g of 3-picolylamine (2.6 mmol) in 10 ml of THF was added 0.42 g of N,N'-carbonyldiimidazole (2.4 mmol) at room temperature, and the mixture was stirred for an hour. To the solution was added 0.58 g of the compound from Example 1, the process (1-4) (1.8 mmol) at room temperature, and the solution was stirred for 3 hours and then left overnight.

20

After diluting with water, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent:ethyl acetate:methanol=10:1) to give 0.77 g of N-[2-(N-tert-

25 butoxycarbonyl)amino]phenyl-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (Yield: 90%) as a white amorphous solid.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.46(9H, s), 4.20(2H, d, J=5.1 Hz),
4.28(2H, d, J=4.3 Hz), 6.10-6.30(2H, m), 7.00-7.25(4H, m), 7.33(1H, d, J=7.3
30 Hz), 7.49-7.54(2H, m), 7.58-7.64(3H, m), 7.75(1H, s), 8.28(1H, br.s), 8.39(1H, d, J=5.1 Hz), 9.65(1H, br.s)

(89-2) To a solution of 0.63 g of the compound from the process (89-1) (1.32 mmol) in 4 ml of dioxane and 2 ml of methanol was added 4 ml of 4N hydrochloride-dioxane, and the mixture was stirred at room temperature for 2 hours. After adding saturated sodium bicarbonate aq., the mixture was
5 extracted with ethyl acetate-methyl ethyl ketone. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with diisopropyl ether to give 0.37 g of N-(2-aminophenyl)-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (Yield: 74.7%) as a brown solid.

10 mp: 167-175°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.27(2H, d, J=5.9 Hz), 4.31(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.57-6.63(3H, m), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.17(1H, d, J=7.3 Hz), 7.32-7.38(3H, m), 7.66(1H, d, J=8.1 Hz),
15 7.93(2H, d, J=8.1 Hz), 8.44(1H, d, J=5.1 Hz), 8.49(1H, d, J=2.1 Hz), 9.63(1H, br.s)

IR(KBr)cm⁻¹ : 3344, 3241, 1645, 1560, 1527, 1505, 1283, 751, 708

20 As described in Example 89, the compounds of Examples 90 to 95 were prepared, each of whose melting point (mp), ¹ H NMR data and/or IR data are shown below.

25 Example 90

N-(2-aminophenyl)-4-[N'-(3-aminophenyl)ureidomethyl]benzamide (Table 1: Compound 24)

30 mp: 206-208°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.35(2H, d, J=5.9 Hz), 4.93(4H,

br.s), 6.13(1H, d, J=7.3 Hz), 6.51-6.62(3H, m), 6.74-6.98(3H, m), 7.12-7.18(1H, m), 7.41(2H, d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.28(1H, s), 9.61(1H, s)

IR(KBr)cm⁻¹ : 3356, 3269, 1640, 1555, 1495, 1458, 1308, 1236, 753

5

Example 91

N-(2-aminophenyl)-4-[N'-(pyridin-3-yl)ureidomethyl]benzamide (Table 1:

10 Compound 87)

mp: 187-190°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.39(2H, d, J=5.9 Hz), 4.89(2H, br.s), 6.59(1H, d, J=7.3, 7.3 Hz), 6.77(1H, d, J=6.6 Hz), 6.88(1H, t, J=5.9 Hz), 6.97(1H, ddd, J=1.5, 6.6, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.26(1H, dd, J=4.4, 8.1 Hz), 7.42(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.1 Hz), 7.89-7.96(1H, m), 8.12(1H, dd, J=1.5, 4.4 Hz), 8.56(1H, d, J=3.0 Hz), 8.85(1H, s), 9.62(1H, s)

20 IR(KBr)cm⁻¹ : 3248, 1663, 1541, 1423, 1280, 1054

Example 92

25 N-(2-aminophenyl)-4-[N'-(3-aminophenyl)thioureidomethyl]benzamide (Table 1: Compound 25)

mp: 123°C(dec.)

30 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.80(2H, d, J=5.1 Hz), 4.87(2H, s), 5.12(2H, s), 6.36(1H, dd, J=1.5, 8.1 Hz), 6.48-6.63(3H, m), 6.78(1H, d, J=6.6 Hz), 6.94-7.00(2H, m), 7.17(1H, d, J=8.1 Hz), 7.42(2H, d, J=8.1 Hz), 7.92-

8.01(3H, m), 9.46(1H, s), 9.61(1H, s)

IR(KBr)cm⁻¹ : 3335, 1616, 1528, 1503, 1456, 1311, 864, 751

5

Example 93

N-(2-aminophenyl)-4-[N'-(3-nitrophenyl)thioureidomethyl]benzamide (Table 1:
Compound 20)

10

mp: 160°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.87(2H, d, J=5.1 Hz), 7.27-
7.33(3H, m), 7.46-7.63(5H, m), 7.89-7.95(2H, m), 8.05(2H, d, J=8.1 Hz),
15 8.70(1H, s), 8.84(1H, t, J=8.9 Hz), 10.37(1H, s)

Example 94

20 N-(2-amino-5-fluorophenyl)-4-[N'-(pyridin-3-yl)methylureidomethyl]benzamide
(Table 1: Compound 112)

mp: (amorphous)

25 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.77(4H, d, J=5.1 Hz), 4.85(2H, s),
6.81(2H, m), 7.16(1H, dd, J=2.9, 10.3 Hz), 7.39(1H, dd, J=5.1, 8.1 Hz), 7.53(2H,
d, J=8.1 Hz), 7.81(1H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 8.51(1H, dd, J=1.5,
5.1 Hz), 8.62(1H, d, J=1.5 Hz), 9.66(1H, s)

30 IR(KBr)cm⁻¹ : 3399, 1730, 1638, 1508, 1444, 1411

Example 95

N-(2-hydroxyphenyl)-4-[N'-(pyridin-3-yl)methylureidomethyl]benzamide (Table 1:
5 Compound 114)

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.43(2H, d, J=6.6 Hz), 4.69(2H, s),
10 6.83(1H, t, J=6.6 Hz), 6.91(1H, d, J=8.1 Hz), 7.68(1H, d, J=6.6 Hz), 7.82(2H, d,
J=8.1 Hz), 8.21(1H, d, J=4.4 Hz), 8.35(1H, d, J=2.2 Hz), 8.81(1H, t, J=6.6 Hz),
9.48(1H, s), 9.75(1H, s)

IR(KBr)cm⁻¹ : 3399, 1664, 1535, 1236, 1064
15

Example 96

Preparation of N-(2-aminophenyl)-4-[2-[N-(pyridin-3-
20 yl)acetamino]ethyl]benzamide (Table 1: Compound 77)

(96-1) To a suspension of 3.40 g of terephthalaldehydic acid (22.6 mmol) in 25
ml of toluene was added 4 ml of thionyl chloride, and the mixture was heated
with stirring at 80°C for 2 hours. After cooling and evaporation, the residue was
25 dissolved in 50 ml of THF to give a solution of the acid chloride. To a solution of
4.16 g of the compound from Example 1, the process (1-2) (20.0 mmol) in 10 ml
of THF was added 6 ml of triethylamine (42.8 mmol) and then the above
solution of the acid chloride was added dropwise under ice-cooling over 30 min.

30 After stirring for 5 hours, to the mixture was added saturated sodium
bicarbonate aq., and the mixture was extracted with ethyl acetate. The organic
layer was washed with saturated brine, dried and evaporated. The residue was

purified by column chromatography on silica gel (gradient elution with chloroform to chloroform:ethyl acetate=10:1) to give 3.42 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-formylbenzamide (Yield: 50.2%) as a light brown solid.

5

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.52(9H, s), 6.77(1H, br.s), 7.16-7.18(2H, m), 7.23-7.26(1H, m), 7.88(1H, d, J=8.8 Hz), 7.98(2H, d, J=8.8 Hz), 8.13(2H, d, J=8.8 Hz), 9.57(1H, br.s), 10.11(1H, br.s)

10 IR(KBr)cm⁻¹ : 3326, 3251, 1707, 1696, 1659, 1603, 1165

(96-2) A suspension of 3.0 g of the compound from the process (96-1) (8.82 mmol) and 4.5 g of ethoxycarbonylmethyl triphenylphosphine (12.9 mmol) in 10 ml of toluene was stirred in a stream of nitrogen at 80°C for 5.5 hours. After

15 cooling, the mixture was diluted with ethyl acetate; washed with saturated sodium bicarbonate, water and saturated brine; dried; and evaporated. The residue was purified by column chromatography on silica gel

(eluent:chloroform:ethyl acetate=20:1) to give 3.3 g of ethyl 4-[N-[2-(N-tert-butoxycarbonyl)aminophenyl]aminocarbonyl]cinnamate (Yield: 91.1%) as a

20 yellow amorphous solid.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.35(3H, t, J=7.3 Hz), 1.52(9H, s), 4.28(2H, q, J=7.3 Hz), 6.52(1H, d, J=15.1 Hz), 6.80(1H, br.s), 7.16-7.25(3H, m), 7.61(2H, d, J=8.1 Hz), 7.71(1H, d, J=15.1 Hz), 7.82(1H, d, 7.3 Hz), 7.98(2H, d, J=8.1 Hz), 9.34 (1H, br.s)

25

(96-3) To a solution of 2.50 g of the compound from the process (96-2) (6.09 mmol) in 30 ml of THF and 40 ml of methanol was added 10% Pd/C (wet, 0.5 g) in a stream of nitrogen, and then stirred in a stream of hydrogen for 30 min.

30 After filling with nitrogen, the mixture was filtered to remove the catalyst, and the filtrate was evaporated. To the residue was added diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 2.23. g of N-[2-(N-

tert-butoxycarbonyl)aminophenyl]-4-(2-ethoxycarbonyl)benzamide (Yield: 88.8%) as a white solid.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.25(3H, t, J=7.3 Hz), 1.52(9H, s),
5 2.65(2H, t, J=7.3 Hz), 3.02(2H, t, J=7.3 Hz), 4.13(2H, q, J=7.3 Hz), 6.77(1H,
br.s), 7.16-7.33(5H, m), 7.78(1H, d, J=8.1 Hz), 7.89(2H, d, J=8.8 Hz), 9.06(1H,
br.s)

(96-4) To a suspension of 2.21 g of the compound from the process (96-3) (5.36
10 mmol) in 10 ml of methanol and 15 ml of water was added 0.37 g of lithium
hydroxide monohydrate (8.82 mmol), and the mixture was stirred at 40°C for 3
hours. After cooling, to the mixture was added 10% hydrochloric acid and the
mixture was extracted with ethyl acetate. The organic layer was washed with
saturated brine, dried and evaporated. To the residue was added diisopropyl
15 ether, and the precipitated solid was filtered and dried to give 1.87 g of N-[2-(N-
tert-butoxycarbonyl)aminophenyl]-4-(2-carboxyethyl)benzamide (Yield: 90.8%)
as a white solid.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.45(9H, s), 2.59(2H, t, J=7.3 Hz),
20 2.91(2H, t, J=7.3 Hz), 7.13-7.20(2H, m), 7.40(2H, d, J=8.1 Hz), 7.54(2H, dd,
J=7.3, 2.1 Hz), 7.88(2H, d, J=8.1 Hz), 8.66(1H, br.s), 9.79(1H, br.s)

(96-5) To a suspension of 0.12 g of the compound from the process (96-4) (0.3
mmol) in 5 ml of benzene were added 0.1 ml of triethylamine (0.7 mmol) and
25 0.3 g of molecular sieves 4A, and the mixture was stirred in a stream of nitrogen
for 0.5 hours. To the mixture was added 0.15 ml of diphenylphosphoryl azide
(0.7 mmol), and the mixture was refluxed with heating for 2 hours. After cooling,
to the mixture was added 0.4 ml of benzyl alcohol (3.8 mmol), and the mixture
was refluxed with heating for additional 2.5 hours. After diluting with ethyl
30 acetate, the reaction mixture was washed with water and saturated brine.

The organic layer was dried and evaporated. The residue was purified by

column chromatography on silica gel (eluent:chloroform:ethyl acetate=4:1) to give 129 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-(N-benzyloxycarbonylamino)ethyl]benzamide (Yield: 88%) as a clear oil.

- 5 ¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.51(9H, s), 2.89(2H, t, J=7.3 Hz), 3.45-3.54(2H, m), 4.80(1H, m), 5.10(2H, s), 6.76(1H, br.s), 7.20-7.38(10H, m), 7.79(1H, d, J=8.8 Hz), 7.89(2H, d, J=8.1 Hz), 9.10(1H, br.s)

- (96-6) To a solution of 129 mg of the compound from the process (96-5) (0.26 mmol) in 10 ml of methanol was added 10% Pd/C (wet, 0.05 g) in a stream of nitrogen, and then stirred in a hydrogen stream for 2 hours. After removing the catalyst, the filtrate was evaporated and dried. The residue was dissolved in 5 ml of dichloromethane. To the solution were added 0.18 g of 3-pyridineacetic acid hydrochloride (1.04 mmol) and then 0.28 g of triethylamine (2.0 mmol), and the mixture was ice-cooled. Under ice-cooling, to the mixture was added 0.17 g of 2-chloro-1,3-dimethylimidazolinium chloride (1.0 mmol), and the mixture was stirred for 2 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent:ethyl acetate:methanol=10:1) to give 50 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-[N-(pyridin-3-yl)acetyl]amino]ethyl]benzamide (Yield: 40%) as a colorless oil.

- 25 ¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.48(9H, s), 2.80(2H, t, J=6.6 Hz), 3.42(2H, m), 3.52(2H, s), 6.33(1H, t-like, J=5.9 Hz), 7.09(2H, d, J=8.1 Hz), 7.14-7.20(2H, m), 7.24(1H, dd, J=4.4, 7.3 Hz), 7.41(1H, dd, J=3.7, 5.9 Hz), 7.50(1H, s), 7.58(1H, dd, J=1.5, 5.9 Hz), 7.69(1H, dd, J=3.7, 5.9 Hz), 7.75(2H, d, J=8.1 Hz), 8.22(1H, d, J=2.1 Hz), 8.44(1H, dd, J=1.5, 4.4 Hz), 9.49(1H, br.s)

- 30 (96-7) To a solution of 50 mg of the compound from the process (96-6) (0.10 mmol) in 2 ml of dioxane and 1 ml of methanol was added 2 ml of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for

2.5 hours. To the mixture was added saturated sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was dried to give 22 mg of N-(2-aminophenyl)-4-[2-[N-(pyridin-3-yl)acetylaminomethyl]benzamide (Yield:

5 59%) as an amorphous solid.

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.70-2.90(4H, m) 3.42(2H, s),
10 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7.16(1H, d, J=7.3 Hz.), 7.29-7.32(3H, m), 7.59(1H, d, J=8.1 Hz), 7.89(1H, d, J=8.1 Hz), 8.22(1H, t-like), 8.41-8.43(2H, m), 9.62(1H, br.s)

15 Example 97

Preparation of N-(2-aminophenyl)-4-[2-[N-(3-picolyl)aminocarbonylmethyl]benzamide (Table 1: Compound 80)

20 (97-1) To a suspension of 0.58 g of the compound from Example 96, the process (96-4) (1.5 mmol) in 5 ml of dichloromethane were added 0.22 g of 3-picolylamine (2.0 mmol) and 0.56 ml of triethylamine (4.0 mmol). Under ice-cooling, to the mixture was added 0.39 g of 2-chloro-1,3-dimethylimidazolium chloride (2.0 mmol) in 5 ml of dichloromethane, and the mixture was stirred for
25 1.5 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform.

The organic layer was washed with water and saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel
30 (eluent:chloroform:methanol:NH.sub.3 aq.=100:10:1) to give 0.71 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-[N-3-picolyl)aminocarbonylmethyl]benzamide (Yield: 94%) as a light brown oil.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.45(9H, s), 2.42(2H, t, J=7.3 Hz),
2.98(2H, t, J=7.3 Hz), 4.32(2H, d, J=6.6 Hz), 6.44(1H, t, J=6.6 Hz), 7.14-
7.27(5H, m), 7.48-7.57 (3H, m), 7.63-7.68(3H, m), 7.90(1H, d, J=2.1 Hz),
5 8.43(1H, dd, J=1.4, 4.4 Hz), 9.86(1H, br.s)

(97-2) To a solution of 0.70 g of the compound from the process (97-1) (1.47
mmol) in 5 ml of dioxane was added 5 ml of 4N hydrochloride-dioxane and then
2 ml of methanol, and the mixture was stirred at room temperature for 2 hours.
10 To the mixture was added saturated sodium bicarbonate aq., and the mixture
was extracted with ethyl acetate. The organic layer was washed with saturated
brine, dried and evaporated. To the residue was added diisopropyl ether, and
the precipitated solid was collected by filtration and dried to give 0.42 g of N-(2-
aminophenyl)-4-[2-[N-(3-picolyl)aminocarbonyl]ethyl]benzamide (Yield: 76.3%)
15 as an opalescent solid.

mp: 168-170°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.47-2.53(2H, m), 2.93(2H, t, J=7.3
20 Hz), 4.27(2H, d, J=5.9 Hz), 4.90(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H,
d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=6.6 Hz), 7.28-7.35(1H,
m), 7.33(2H, d, J=8.1 Hz), 7.49(1H, dd, J=2.1, 5.9 Hz), 7.89(2H, d, J=8.1 Hz),
8.39-8.44(3H, m), 9.62(1H, br.s)

25 IR(KBr)cm⁻¹ : 3313, 1641, 1523, 1457, 1300, 748, 713

Example 98

Preparation of N-(2-aminophenyl)-4-[(pyridin-3-yl)methylaminocarbonyloxymethyl]benzamide (Table 1: Compound 85)

5

(98-1) To a solution of 1.99 g of methyl 4-hydroxymethylbenzoate (12.0 mmol) in 20 ml of THF were added 1.78 g of N,N'-carbonyldiimidazole (11.0 mmol) at room temperature, and the solution was stirred for an hour. To the solution were added 1.08 g of 3-picolylamine (10.0 mmol) at room temperature, and the mixture was stirred for 3.5 hours and left overnight. Water was added to the solution, and the mixture was extracted with ethyl acetate.

10

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give 2.76 g of N-(4-methoxycarbonyl)benzyloxycarbonyl-3-picolylamine (Yield: 91.9%) as a white waxy solid.

15

^1H NMR(270 MHz, CDCl_3) δ . ppm: 3.91(3H, s), 4.40(2H, d, $J=5.9$ Hz), 5.18(2H, s), 5.50(1H, br.s), 7.24-7.28(1H, m), 7.40(2H, d, $J=8.1$ Hz), 7.65(1H, d, $J=7.3$ Hz), 8.02(2H, d, $J=8.8$ Hz), 8.50-8.53(2H, m)

20

(98-2) To a suspension of 2.40 g of the compound from the process (98-1) (8.0 mmol) in 10 ml of methanol and 20 ml of water was added 0.42 g of lithium hydroxide monohydrate (10.0 mmol), and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added 10% hydrochloric acid to acidified to pH 2 to 4, and the precipitated solid was collected by filtration and dried to give 1.83 g of N-(4-carboxy)benzyloxycarbonyl-3-picolylamine (79.9%) as a white solid.

25

^1H NMR(270 MHz, $\text{DMSO}-d_6$) δ . ppm: 4.24(2H, d, $J=5.9$ Hz), 5.13(2H, s), 7.33-7.38 (1H, m), 7.46(2H, d, $J=8.1$ Hz), 7.94(2H, d, $J=8.1$ Hz), 7.95-8.01(1H, m), 8.46(1H, d, $J=5.1$ Hz), 8.49(1H, d, $J=1.5$ Hz), 13.0(1H, br.s)

30

(98-3) To a suspension of 1.26 g of the compound from the process (98-2) (4.4 mmol) in 20 ml of dichloromethane were slowly added 1.0 ml of oxalyl chloride (11.4 mmol) and then several drops of DMF. The reaction mixture was stirred at room temperature for 10 min. and at 40°C for additional 30 min. After cooling, the mixture was evaporated and the excess oxalyl chloride was removed by evaporation with toluene. To the residue was added 10 ml of dichloromethane. Under ice-cooling, to the mixture was added dropwise a solution of 0.83 g of the compound from Example 1, the process (1-2) (4.0 mmol) in 8 ml of dichloromethane and 8 ml of pyridine, and the solution was warmed to room temperature with stirring for 7 hours and left overnight.

To the mixture was added saturated sodium bicarbonate, and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. Toluene was added to the residue to azeotropically remove the excess pyridine. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give 1.40 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[(pyridin-3-yl)methylaminocarbonyloxymethyl]benzamide (Yield: 73.4%) as a light brown solid.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.51(9H, H), 4.40(2H, d, J=5.9 Hz), 5.19(2H, s), 5.56(1H, m), 7.07(1H, br.s), 7.14-7.31(4H, m), 7.43(2H, d, J=8.1 Hz), 7.65(1H, d, J=8.1 Hz), 7.76(1H, d, J=7.3 Hz), 7.95(2H, d, J=8.1 Hz), 8.52(2H, d, J=4.1 Hz), 9.32(1H,br.s)

(98-4) To a solution of 1.00 g of the compound from the process (98-3) (2.10 mmol) in 10 ml of dioxane and 2 ml of methanol was added 9 ml of 4N hydrochloric acid-dioxane at room temperature, and the mixture was stirred for 2 hours. To the mixture was added saturated sodium bicarbonate and the mixture was extracted with ethyl acetate-methyl ethyl ketone (1:1). The organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol-diisopropyl ether, and the precipitated solid was collected

by filtration and dried to give 0.79 g of N-(2-aminophenyl)-4-[(pyridin-3-yl)methylaminocarbonyloxymethyl]benzamide (Yield: quantitative) as a white solid.

5 mp: 139-141°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.25(2H, d, J=5.9 Hz), 4.90(2H, s), 5.13(2H, s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.36(1H, dd, J=4.4, 8.1 Hz), 7.47(2H, d, J=8.1 Hz), 7.67(1H, d, J=8.1 Hz), 7.97(2H, d, J=7.3 Hz), 7.90-8.00(1H, m), 8.46(1H, dd, J=1.5, 5.1 Hz), 8.49(1H, d, J=2.1 Hz), 9.65(1H, br.s)

10

IR(KBr)cm⁻¹ : 3326(br.), 1694, 1637, 1526, 1458, 1147, 750, 712

15

Example 99

Preparation of N-(2-aminophenyl)-4-[3-(imidazol-1-yl)propylaminocarbonyloxymethyl]benzamide (Table 1: Compound 215)

20

The title compound was prepared as described in Example 98.

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.80-1.89(2H, m), 2.94-3.02(2H, m), 3.98(2H, t, J=7.3 Hz), 4.88(2H, s), 5.11(2H, s), 6.55-6.63(1H, m), 6.76-6.97(3H, m), 7.10-7.18(2H, m), 7.43-7.48(3H, m), 7.61(1H, s), 7.98(2H, d, J=8.1 Hz), 9.66(1H, s)

25

30

Example 100

Preparation of N-(2-aminophenyl)-4-(phenylacetyl-amino)benzamide (Table 1: Compound 2)

5

(100-1) To a solution of 16.6 g of the compound from Example 1, the process (1-2) (80 mmol) in 120 ml of dichloromethane was added 16.8 ml of triethylamine (120 mmol) and then, was slowly added a solution of 16.0 g of 4-nitrobenzoyl chloride (86.4 mmol) in 40 ml of dichloromethane, and the solution was stirred for 7 hours. To the solution was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform.

10

The organic layer was washed with 1N hydrochloric acid, saturated sodium bicarbonate and saturated brine; dried; and evaporated. The residue was washed with diisopropyl ether to give 28.0 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-nitrobenzamide (Yield: 98%) as a light yellow solid.

15

^1H NMR(270 MHz, CDCl_3) δ . ppm: 1.53(9H, s), 7.17-7.29(4H, m), 7.85(1H, br.d, $J=7.3$ Hz), 8.17(2H, d, $J=8.8$ Hz), 8.32(2H, d, $J=8.8$ Hz), 9.88(1H, br.s)

20

(100-2) To a solution of 24.0 g of the compound from the process (100-1) (67.2 mmol) in 80 ml of THF and 80 ml of methanol was added 2.4 g of 10% Pd/C (wet) in a stream of nitrogen, and the mixture was stirred in a stream of hydrogen for 1.5 hours. After cease of absorption of hydrogen, the catalyst was removed by filtration and the filtrate was evaporated. To the residue were added diisopropyl ether and ethyl acetate, and the precipitated solid was collected by filtration and dried to give 18.96 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-aminobenzamide (Yield: 86%) as a white solid.

25

30

^1H NMR(270 MHz, $\text{DMSO}-d_6$) δ . ppm: 1.46(9H, s), 5.84(2H, s), 6.61(2H, d,

J=8.8 Hz), 7.10-7.18(2H, m), 7.46-7.55(2H, m), 7.68(2H, d, J=8.8 Hz), 8.67(1H, s), 9.49(1H, s)

(100-3) To a solution of 1.6 g of the compound from the process (100-2) (4.88 mmol) in 15 ml of dichloromethane were added 0.8 ml of pyridine (9.9 mmol) and 0.96 ml of phenylacetyl chloride (7.26 mmol), and the solution was stirred for one day. After completion of the reaction, water was added and the precipitated crystals were collected by filtration to give 1.66 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-(phenylacetylaminobenzamide (Yield: 76%).

(100-4) To a solution of 1 g of the compound from the process (100-3) (2.24 mmol) in 25 ml of acetonitrile was added 0.88 ml of iodotrimethylsilane (6.18 mmol) at room temperature, and the solution was stirred for 3 hours. After completion of the reaction, the solution was concentrated. The residue was recrystallized from methanol to give 0.29 g of N-(2-aminophenyl)-4-(phenylacetylaminobenzamide (Yield: 38%) as white crystals.

mp: 232-237°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.69(2H, s), 4.90(2H, s), 6.60(1H, t, J=7.3 Hz), 6.77(1H, d, J=7.3 Hz), 6.96(1H, t, J=7.3 Hz), 7.15(1H, d, J=7.4 Hz), 7.22-7.35(5H, m), 7.72(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.8 Hz), 9.57(1H, s), 10.43(1H, s)

IR(KBr)cm⁻¹ : 2937, 2764, 1660, 1598, 1506, 1459

As described in Example 100, the compounds of Examples 101 to 128 were prepared, each of whose melting point (mp), ¹ H NMR data and/or IR data are shown below.

Example 101

N-(2-aminophenyl)-4-[(4-phenylbutanoyl)amino]benzamide (Table 1: Compound 4)

5

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.91(2H, hep, J=7.3 Hz), 2.37(2H, t, J=7.3 Hz), 2.64(2H, t, J=7.3 Hz), 5.0(2H, br.s), 6.61(1H, t, 7.0 Hz), 6.79(1H, dd, J=1.5, 8.1 Hz), 6.97(1H, t, J=7.0 Hz), 7.10-7.40(6H, m), 7.71(2H, d, J=8.8 Hz), 7.94(2H, d, J=8.8 Hz), 9.57(1H, s), 10.15(1H, s)

10

IR(KBr)cm⁻¹ ; 3344, 1687, 1603, 1542, 1460, 1315, 1033, 842, 737

15

Example 102

N-(2-aminophenyl)-4-[(4-chlorophenylacetyl)amino]benzamide (Table 1: Compound 15)

20

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.72(2H, s), 7.29-7.43(8H, m), 7.77(2H, d, J=8.8 Hz), 8.00(2H, d, J=8.8 Hz), 10.29(1H, s), 10.52(1H, s)

25

IR(KBr)cm⁻¹ : 3300, 2868, 1664, 1638, 1520

30

Example 103

N-(2-aminophenyl)-4-[(2-nitrophenylacetyl)amino]benzamide hydrochloride
(Table 1: hydrochloride of Compound 19)

5

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.20(2H, s), 7.20-7.30(3H, m), 7.40-7.45(1H, m), 7.60(2H, d), 7.71-7.77(3H, m), 8.02-8.10(4H, m), 10.27(1H, br.s),
10 10.64(1H, br.s)

IR(KBr)cm⁻¹ : 3263, 1676, 1647, 1518, 1184, 759

15 Example 104

N-(2-aminophenyl)-4-[(4-nitrophenylacetyl)amino]benzamide (Table 1:
Compound 21)

20 mp: 222-226°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.90(2H, s), 4.96(2H, br.s), 6.60(1H, dt, J=1.5, 6.6 Hz), 6.78(1H, dd, J=1.5, 6.6 Hz), 6.97(1H, dt, J=1.5, 6.6 Hz), 7.15(1H, dd, J=1.5, 6.6 Hz), 7.63(2H, d, J=8.8 Hz), 7.71(2H, d, J=8.8 Hz),
25 7.95(2H, d, J=8.8 Hz), 8.22(2H, d, J=8.8 Hz), 9.59(1H, s), 10.54(1H, s).

IR(KBr)cm⁻¹ : 3395, 3334, 1671, 1630, 1519, 1346

Example 105

N-(2-aminophenyl)-4-[(2-aminophenylacetyl)amino]benzamide (Table 1:
Compound 22)

5

mp: 177-182°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.54(2H, s), 4.88(2H, br.s), 5.09(2H, br.s), 6.55(1H, dd, J=6.6, 7.3 Hz), 6.59(1H, dd, J=7.3, 7.3 Hz), 6.68(1H, d, J=7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.96(2H, dd, J=7.3, 7.3 Hz), 7.06(1H, d, J=6.6 Hz), 7.15(1H, d, J=7.3 Hz), 7.71(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.8 Hz), 9.57(1H, br.s), 10.39(1H, br.s)

10

IR(KBr)cm⁻¹ : 3374, 3256(br.), 1683, 1597, 1503, 1317, 1262, 1180, 1153, 747

15

Example 106

N-(2-aminophenyl)-4-[(4-aminophenylacetyl)amino]benzamide (Table 1:
Compound 26)

20

mp: 219-226°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.46(2H, s), 4.93(4H, br.s), 6.52(2H, d, J=8.1 Hz), 6.59(1H, dt, J=1.5, 7.3 Hz), 6.77(1H, dd, J=1.4, 7.3 Hz), 6.97(1H, dt, J=1.4, 7.3 Hz), 6.99(2H, d, J=8.1 Hz), 7.15(1H, dd, J=1.5, 7.3 Hz), 7.70(2H, d, J=8.8 Hz), 7.93(2H, d, J=8.8 Hz)

25

IR(KBr)cm⁻¹ : 3278, 3032, 1675, 1628, 1516

30

Example 107

N-(2-aminophenyl)-4-[(4-methoxyphenylacetyl)amino]benzamide (Table 1:
Compound 32)

5

mp: (amouphous)

¹ H NMR(270 MHz, DMSO-d6) .delta. ppm: 3.62(2H, s), 3.74(3H, s), 6.90(2H, d,
J=8.8 Hz), 7.26(2H, d, J=8.8 Hz), 7.30(3H, m), 7.39(1H, m), 7.77(2H, d, J=8.8
10 Hz), 7.99(2H, d, J=8.8 Hz), 10.26(1H, s), 10.44(1H, s)

IR(KBr)cm-1 : 3300, 2759, 1670, 1638, 1514, 1250

15 Example 108

N-(2-aminophenyl)-4-[[4-(N,N-dimethylamino)phenylacetyl]amino]benzamide
(Table 1: Compound 53)

20 mp: 140°C

¹ H NMR(270 MHz, DMSO-d6) .delta. ppm: 3.04(6H, s), 3.67(2H, s), 7.16(2H, d,
J=8.0 Hz), 7.29-7.40(6H, m), 7.76(2H, d, J=8.8 Hz), 7.99(2H, d, J=8.8 Hz),
10.29(1H, s), 10.47(1H, s)

25

IR(KBr)cm-1 : 3244, 2951, 2639, 1647, 1599, 1507

30

Example 109

N-(2-aminophenyl)-4-[(4-trifluoromethylphenylacetyl)amino]benzamide (Table 1:
Compound 43)

5

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.84(2H, s), 6.89(1H, t, J=7.4 Hz),
7.00(1H, d, J=7.4 Hz), 7.11(1H, t, J=7.4 Hz), 7.25(1H, d, J=7.4 Hz), 7.57(2H, d,
10 J=8.8 Hz), 7.71(2H, d, J=8.8 Hz), 7.73(2H, d, J=8.8 Hz), 7.97(2H, d, J=8.8 Hz),
9.87(1H, s), 10.54(1H, s)

IR(KBr)cm⁻¹ : 3260, 1664, 1605, 1521, 1327, 1119

15

Example 110

N-(2-aminophenyl)-4-[(pyridin-2-yl)acetylamino]benzamide
dihydrochloride(Table 1: hydrochloride of Compound 174)

20

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.60(2H, s), 7.30-7.46(3H, m),
7.56(1H, d, J=7.4 Hz), 7.79(2H, d, J=8.8 Hz), 7.95(1H, t, J=6.6 Hz), 8.01(1H, d,
25 J=7.4 Hz), 8.11(2H, d, J=8.8 Hz), 8.49(1H, t, J=7.4 Hz), 8.87(1H, d, J=5.1 Hz),
10.46(1H, s)

30

Example 111

N-(2-aminophenyl)-4-[(pyridin-3-yl)acetylamino]benzamide
dihydrochloride (Table 1: hydrochloride of Compound 68)

5

mp: 182-189°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.12(2H, s), 7.29-7.59(4H, m),
7.80(2H, d, J=8.8 Hz), 8.05(1H, m), 8.11(2H, d, J=8.8 Hz), 8.57(1H, d, J=8.1
10 Hz), 8.85(1H, d, J=5.2 Hz), 8.95(1H, s), 10.25(1H, s), 10.48(1H, s)

Example 112

15 N-(2-aminophenyl)-4-[[3-(pyridin-3-yl)propanoyl]amino]benzamide (Table 1:
Compound 69)

mp: 184-186°C

20 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.80(2H, t, J=7.3 Hz), 3.08(2H, t,
J=7.3 Hz), 6.87(1H, t, J=8.0 Hz), 6.99(1H, dd, J=1.4, 8.0 Hz), 7.11(1H, dt, J=1.4,
8.0 Hz), 7.25(1H, d, J=8.0 Hz), 7.70(2H, d, J=8.8 Hz), 7.77(1H, dd, J=5.8, 8.0
Hz), 7.96(2H, d, J=8.8 Hz), 8.22(1H, d, J=8.0 Hz), 8.75(1H, d, J=1.4 Hz),
9.83(1H, s), 10.25(1H, s)

25

30

Example 113

N-(2-aminophenyl)-2-chloro-4-[3-(pyridin-3-yl)propanoylamino]benzamide
(Table 1: Compound 123)

5

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.70(2H, t, J=8.1 Hz), 2.96(2H, t, J=7.3 Hz), 4.74(2H, br.s), 6.60(1H, t, J=6.6 Hz), 6.78(1H, d, J=6.6 Hz), 6.95(1H, t, J=6.6 Hz), 7.19(1H, dd, J=1.5, 7.3 Hz), 7.29(1H, dd, J=5.1, 7.3 Hz), 7.66(2H, d, J=8.8 Hz), 7.92(2H, d, J=8.8 Hz), 8.48(1H, d, J=2.2 Hz), 9.37(1H, s), 10.00(1H, s)

15

IR(KBr)cm⁻¹ : 3273, 1675, 1519, 1315, 1181, 852, 747

Example 114

N-(2-aminophenyl)-4-[[N-(pyridin-3-yl)methyl-N-trifluoroacetylaminio]acetylamino]benzamide (Table 1: Compound 107)

20

mp: 145°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.18 and 4.42(total 2H, s), 4.73 and 4.83(total 2H, s), 4.87(2H, br.s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.35-7.45(1H, m), 7.66(2H, d, J=5.9 Hz), 7.70-7.80(1H, m), 7.90-8.00(2H, m), 8.51-8.55(1H, m), 8.58(1H, s), 9.60(1H, br.s), 10.36 and 10.43(total 1H, br.s)

30

Example 115

N-(2-aminophenyl)-4-[[N-(pyridin-3-yl)methylamino]acetylamino]benzamide
(Table 1: Compound 105)

5

mp: 160°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.30(2H, s), 3.79(2H, s), 4.88(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.74(2H, d, J=8.8 Hz), 7.80(1H, d, J=7.3 Hz), 7.95(2H, d, J=8.1 Hz), 8.46(1H, d, J=3.7 Hz), 8.57(1H, s), 9.57(1H, s), 10.08(1H, br.s)

10

IR(KBr)cm⁻¹ : 3298, 1693, 1637, 1602, 1544, 1454, 1262, 848, 762

15

Example 116

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methyloxamoylamino]benzamide (Table 1:
Compound 104)

20

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.43(2H, d, J=6.6 Hz), 4.90(2H, br.s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, ddd, J=1.5, 6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.37(1H, dd, J=4.4, 8.1 Hz), 7.73(1H, d, J=8.1 Hz), 7.96 and 7.96(4H, AA'BB', J=9.4 Hz), 8.47(1H, dd, J=1.5, 5.1 Hz), 8.56(1H, d, J=1.5 Hz), 9.59 (1H, s), 9.67(1H, t, J=6.6 Hz), 10.92(1H, br.s)

25

IR(KBr)cm⁻¹ : 3299, 1644, 1518, 1320, 1119, 748

30

Example 117

N-(2-aminophenyl)-4-[[N-(pyridin-3-yl)methyl-N-nicotinoylamino]acetylamino]benzamide (Table 1: Compound 106)

5

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.11(major 2H, s), 4.26(minor 2H, s), 4.75(major 2H, s), 4.65(minor 2H, s), 4.88(total 2H, br.s), 6.60(total 1H, dd, J=7.3, 8.1 Hz), 6.78(total 1H, d, J=7.3 Hz), 6.97(total 1H, dd, J=7.3, 8.1 Hz), 7.15(total 1H, d, J=8.1 Hz), 7.41-7.95(total 8H, m), 8.46-8.52(total 1H, m), 8.63-8.70(total 2H, m), 9.59(total 1H, s), 10.22(major 1H, br.s), 10.37(minor 1H, br.s)

10

IR(KBr)cm⁻¹ : 3269, 1701, 1637, 1603, 1534, 1506, 1312, 1254, 752

15

Example 118

N-(2-aminophenyl)-4-[[4-(pyridin-3-yl)butanoyl]amino]benzamide (Table 1: Compound 70)

20

mp: 165-167°C(dec.)

25

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.88-1.99(2H, m), 2.68(2H, t, J=7.3 Hz), 2.39(2H, t, J=7.3 Hz), 6.78-6.81(1H, m), 6.94-6.99(1H, m), 7.15-7.18(1H, m), 7.34-7.39(1H, m), 7.69-7.72(3H, m), 7.94(2H, d, J=8.8 Hz), 8.43-8.48(2H, m)

IR(KBr)cm⁻¹ : 3291, 1660, 1626, 1308, 1261, 1182, 1027, 825, 747

30

Example 119

N-(2-aminophenyl)-4-[[N-(pyridin-3-yl)methyl-N-methylamino]acetylamino]benzamide (Table 1: Compound 108)

5

mp: 154-155°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.28(3H, s), 3.27(2H, s), 3.71(2H, s), 4.88(2H, br.s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=8.1 Hz), 7.38(1H, dd, J=2.9, 8.1 Hz), 7.77(2H, d, J=8.8 Hz), 7.75-7.85(1H, m), 7.95(2H, d, J=8.8 Hz), 8.47(1H, d, J=1.5 Hz), 8.49(1H, s), 9.56(1H, s), 10.62(1H, br.s)

15 Example 120

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetylamino]benzamide (Table 1: Compound 65)

20 mp: 175-179°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.86(2H, s), 4.90(2H, br.s), 6.60(1H, d, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=8.1 Hz), 7.34-7.47(2H, m), 7.76(2H, d, J=8.8 Hz), 7.98(2H, d, J=8.8 Hz), 8.22(1H, d, J=3.6 Hz), 8.39(1H, d, J=2.9 Hz), 9.60(1H, br.s), 10.40(1H, br.s)

IR(KBr)cm⁻¹ : 3321, 1655, 1530, 1276, 1231, 1068,

Example 121

N-(2-aminophenyl)-4-[4-(pyridin-3-yl)-1,4-dioxobutylamino]benzamide (Table 1: Compound 99)

5

mp: 190-194°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.08(2H, t, J=6.4 Hz), 3.41(2H, t, J=6.4 Hz), 4.86(2H, s), 6.59(1H, t, J=5.6 Hz), 6.78(1H, d, J=7.9 Hz), 6.96(1H, t, J=7.4 Hz), 7.15(1H, d, J=7 Hz), 7.58(1H, dd, J=4.9, 7.9 Hz), 7.70(2H, d, J=8.9 Hz), 7.94(2H, d, J=8.9 Hz), 8.35(1H, d, J=7.9 Hz), 8.81(1H, d, J=4 Hz), 9.18(1H, s), 9.56(1H, s), 10.32(1H, s)

15

IR(KBr)cm⁻¹ : 3317, 1691, 1652, 1601, 1522, 1312, 982, 847, 764, 701

Example 122

N-(2-aminophenyl)-4-[3-[N-(pyridin-3-yl)amino]-1,3-dioxopropylamino]benzamide (Table 1: Compound 94)

20

mp: 196°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.57(2H, s), 4.87(2H, s), 6.57-6.62(1H, m), 6.76-6.79(1H, m), 6.94-6.99(1H, m), 7.14-7.17(1H, m), 7.33-7.38(1H, m), 7.73(2H, d, J=8.8 Hz), 7.97(2H, d, J=8.8 Hz), 8.05-8.08(1H, m), 8.27-8.30(1H, m), 8.75-8.76(1H, m), 9.59(1H, s), 10.44(1H, s), 10.47(1H, s)

25

IR(KBr)cm⁻¹ : 3410, 3315, 1685, 1655, 1625, 1536, 1428, 1362, 1263, 1201, 744

30

Example 123

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxyacetylamino]-3-methylbenzamide

5 (Table 1: Compound 102)

mp: 178-181°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.28(3H, s), 4.22(2H, s), 4.71(2H, s), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.43(1H, dd, J=4.4, 8.1 Hz), 7.71(1H, d, J=8.1 Hz), 7.79-7.89(3H, m), 8.54(1H, dd, J=1.5, 4.4 Hz), 8.66(1H, d, J=1.5 Hz), 9.36(1H, br.s), 9.60(1H, br.s)

15 IR(KBr)cm⁻¹ : 3394, 3269, 1683, 1630, 1593, 1521, 1460, 1131, 750, 716

Example 124

20 N-(2-aminophenyl)-4-[N-(thiophen-3-yl)methoxyacetylamino]benzamide (Table 1: Compound 204)

mp: 186-189°C

25 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.11(2H, s), 4.63(2H, s), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7.12-7.19(2H, m), 7.53-7.57(2H, m), 7.78(2H, d, J=8.8 Hz), 7.95(2H, d, J=8.8 Hz), 9.58(1H, br.s), 10.04(1H, br.s)

30 IR(KBr)cm⁻¹ : 3341, 3248, 1694, 1631, 1611, 1506, 1314, 1126

Example 125

- 5 N-(2-aminophenyl)-4-[N-methyl-N-(pyridin-3-yl)methoxyacetylaminobenzamide
(Table 1: Compound 103)

mp: 180-183°C(dec.)

- 10 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.24(3H, s), 4.08(2H, br.s), 4.50(2H, s), 4.94(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.79(1H, d, J=8.1 Hz), 6.98(1H, dd, J=7.3, 8.1 Hz), 8.03(1H, d, J=8.1 Hz), 8.48-8.50(2H, m), 9.72(1H, br.s)

IR(KBr)cm⁻¹ : 3395, 3283, 1683, 1639, 1604, 1506, 1459, 1307, 1124

15

Example 126

- 20 N-(2-aminophenyl)-4-[N-(pyridin-2-yl)methoxyacetylaminobenzamide (Table 1:
Compound 176)

mp: 171-173°C

- 25 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.26(2H, s), 4.74(2H, s), 4.89(2H, br.s), 6.60(1H, dd, J=6.6, 8.1 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, ddd, J=1.5, 7.3, 8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.35(1H, dd, J=5.1, 6.6 Hz), 7.80(2H, d, J=8.1 Hz), 7.80-7.89(1H, m), 7.97(2H, d, J=8.1 Hz), 8.59(1H, d, J=4.4 Hz), 9.59(1H, br.s), 10.30(1H, br.s)

- 30 IR(KBr)cm⁻¹ : 3391, 3258, 1678, 1629, 1593, 1517, 1128, 767, 742

Example 127

5

N-(2-aminophenyl)-4-[N-(N-nicotinoylamino)acetylamino]benzamide (Table 1:
Compound 97)

mp: 218-220°C(dec.)

10

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.13(2H, d, J=5.9 Hz), 4.89(2H, s),
6.59(1H, dd, J=7.3, 7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.96(1H, dd, J=7.3, 8.1 Hz),
7.15(1H, d, J=7.3 Hz), 7.55(1H, dd, J=5.1, 8.1 Hz), 7.73(2H, d, J=8.8 Hz),
7.96(2H, d, J=8.8 Hz), 8.25(1H, d, J=8.1 Hz), 8.74(1H, d, J=5.1 Hz), 9.07(1H, d,
15 J=1.5 Hz), 9.13(1H, t-like, J=5.9 Hz), 9.58(1H, s), 10.36(1H, s)

Example 128

20 N-(2-aminophenyl)-5-[3-(pyridin-3-yl)propionamide]benzofuran-2-carboxamide
(Table 3: Compound 1)

mp: 267-272°C

25 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 2.51(2H, t, J=7.3 Hz), 2.97(2H, t,
J=7.3 Hz), 6.61(1H, dd, J=8.1, 8.8 Hz), 6.80(1H, dd, J=1.5, 8.1 Hz), 6.99(1H,
dd, J=8.1, 8.8 Hz), 7.20(1H, dd, J=1.5, 8.1 Hz), 7.32(1H, dd, J=5.2, 8.1 Hz),
7.49(1H, dd, J=1.5, 8.8 Hz), 7.61(1H, d, J=8.8 Hz), 7.67(1H, s), 7.70(1H, m),
8.15(1H, d, J=1.5 Hz), 8.40(1H, dd, J=1.5, 5.2 Hz), 8.51(1H, d, J=1.5 Hz),
30 9.84(1H, s), 10.1(1H, s)

IR(KBr)cm⁻¹ : 3333, 3272, 1666, 1583, 1561, 1458, 1314, 1247, 1143, 807,

746, 713

Example 129

5

Preparation of N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)oxypropionyl]amino]benzamide (Table 4: Compound 2)

(129-1) In 10 ml of dichloromethane were dissolved 0.34 g of the compound
10 from Example 47, the process (47-2) (1.2 mmol) and 0.34 g of the compound from Example 100, the process (100-2) (1.0 mmol), and then 0.5 ml of triethylamine (3.6 mmol). Under ice-cooling, to the solution was added 0.21 g of 2-chloro-1,3-dimethylimidazolidinium chloride (1.24 mmol) in 5 ml of dichloromethane, and the solution was stirred under ice-cooling for 2 hours.
15 After neutralizing with saturated sodium bicarbonate aq., the mixture was diluted with water and extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:methanol=10:1) to give 0.68 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-[N-[2-(pyridin-3-yl)oxypropionyl]amino]benzamide as a mixture with 1,3-dimethyl-2-imidazolinone.
20

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.52(9H,s), 1.70(3H, d, J=6.6 Hz), 4.84(1H, q, J=6.6 Hz), 6.89(1H, br.s), 7.12-7.31(6H, m), 7.68(2H, d, J=8.8 Hz), 7.79(1H, d, J=8.1 Hz), 7.96(2H, d, J=8.8 Hz), 8.34(1H, d, J=2.9, 2.9 Hz),
25 8.43(1H, d, J=1.5 Hz), 9.25(1H, br.s)

(129-2) To a solution of 0.68 g of the compound from the process (129-1) in 5 ml of dichloromethane was added 10 ml of 15% (vol/vol) trifluoroacetic acid/dichloromethane, and the solution was stirred at room temperature for 4.5
30 hours. After neutralizing the solution with saturated sodium bicarbonate aq., dichloromethane was removed by evaporation. The solution was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and

evaporated. To the residue were added methanol and diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 0.22 g of N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)oxypropionyl]amino]benzamide (Yield: 58% for the 2 steps) as an opalescent solid.

5

mp: 193-196°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.60(3H, d, J=6.6 Hz), 4.88(2H, br.s), 5.04(1H, q, J=6.6 Hz), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=8.1 Hz),
10 6.97(1H, dd, J=7.3, 8.1 Hz), 7.15(1H, d, J=7.3 Hz), 7.32-7.39(2H, m), 7.75(2H, d, J=8.8 Hz), 7.96(2H, d, J=8.1 Hz), 8.20(1H, dd, J=1.5, 3.7 Hz), 8.35(1H, d, J=2.1 Hz), 9.59(1H, br. s), 10.44(1H, br. s)

15 Example 130

Preparation of N-(2-aminophenyl)-4-[(pyridin-3-yl)methoxyacetyl]amino]benzamide (Table 1: Compound 101)

20 (130-1) To a suspension of 4.4 g of sodium hydride (60% oil dispersion; 110 mmol) in 300 ml of THF were added dropwise 10.91 g of 3-pyridinemethanol (100 mmol) in 20 ml of THF at room temperature, and the mixture was stirred at room temperature for 2 hours. The resulting white suspension was ice-cooled, and 19.51 g of tert-butyl bromoacetate (100 mmol) in 20 ml of THF was added
25 dropwise, maintaining the inner temperature within 10 to 12°C The suspension was warmed to room temperature with stirring for 3 hours, and then left overnight. After adding water and saturated sodium bicarbonate aq., the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column
30 chromatography on silica gel (gradient elution with n-hexane:ethyl acetate=1:1 to ethyl acetate) to give 7.56 g of tert-butyl (pyridin-3-yl)methoxyacetate (33.8%) as a light brown oil.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.49(9H,9s), 4.03(2H, s), 4.64(2H, s), 7.30(1H, dd, J=4.9, 7.3 Hz), 7.76(1H, d, J=7.3 Hz), 8.56(1H, d, J=4.9 Hz), 8.60(1H, s)

5

(130-2) Under ice-cooling, 12 ml of trifluoroacetic acid was added to 3.5 g of the compound from the process (130-1) (15.7 mmol), and the solution was stirred at room temperature for 6 hours. Part of trifluoroacetic acid was removed by evaporation to give a mixture of (pyridin-3-yl)methoxyacetic acid and

10 trifluoroacetic acid (6.5 g). The mixture was dissolved in 70 ml of dichloromethane. To the solution was added 25 ml of pyridine and then, was slowly added dropwise under ice-cooling, 2.37 g of 2-chloro-1,3-dimethylimidazolinium chloride (14.0 mmol) in 20 ml of dichloromethane over 30 min, and the solution was stirred under ice-cooling for additional 5 hours. To the
15 solution was added saturated sodium bicarbonate aq., and stirring was continued until foaming ceased. The mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (gradient elution with ethyl acetate to ethyl acetate:methanol=10:1) to give 4.78 g of N-[2-(N-tert-
20 butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)methoxyacetylamino]benzamide (Yield: 62%) as a 1:1 (molar ratio) mixture with DMI (1,3-dimethyl-2-imidazolinone).

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.51(9H, s), 4.15(2H, s), 4.70(2H, s), 6.92(1H, br.s), 7.15-7.29(3H, m), 7.37(1H, dd, J=7.3, 5.1 Hz), 7.67(2H, d, J=8.8 Hz), 7.71-7.79(2H, m), 7.96(2H, d, J=8.8 Hz), 8.41(1H, s), 8.62-8.66(2H, m), 9.23(1H, br.s)

(130-3) To a solution of 2.39 g of the compound from the process (130-2) (4.0
30 mmol) in 28 ml of dichloromethane was added 55 ml of 15% (vol/vol) trifluoroacetic acid/dichloromethane, and the solution was stirred at room temperature for 7 hours. The solution was neutralized with saturated sodium

bicarbonate, and then water was added. The reaction mixture was stirred at room temperature and extracted with a 2:1 mixture of ethyl acetate-methyl ethyl ketone, a 2:1 mixture of ethyl acetate-THF, and ethyl acetate, in sequence. The combined organic layer was washed with saturated brine and dried over
5 anhydrous sodium sulfate. After removing the dehydrating reagent by filtering, the filtrate was concentrated. To the residue thus obtained were added methanol and diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 1.29 g of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxyacetyl amino]benzamide (Yield: 85.6%) as a dark brown solid.

10 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.19(2H, s), 4.68(2H, s), 4.90(2H, br.s), 6.60(1H, ddd, J=1.5, 7.3, 8.1 Hz), 6.78(1H, dd, J=1.5, 8.1 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7.15(1H, d, J=7.3 Hz), 7.42(1H, dd, J=4.4, 8.1 Hz), 7.77(2H, d, J=8.8 Hz), 7.85(1H, d, J=7.3 Hz), 7.96(2H, d, J=8.8 Hz), 8.54(1H, dd, J=1.5,
15 5.1 Hz), 8.63(1H, s), 9.58(1H, s), 10.09(1H, s)

IR(KBr)cm⁻¹ : 3403, 3341, 3250, 1694, 1630, 1610, 1506, 1314, 1259, 1118, 764

20 Example 131

Preparation of N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)methoxypropionyl]amino]benzamide (Table 4: Compound 1)

25 (131-1) To a suspension of 1.24 g of sodium hydride (60% oil dispersion; 31 mmol) in 90 ml of THF were added dropwise 3.27 g of 3-pyridinemethanol (30 mmol) in 10 ml of dry THF at room temperature over 5 min. The resulting white suspension was stirred at room temperature for an hour, to which was then
30 added dropwise 6.27 g of tert-butyl 2-bromopropionate (30 mmol) in 10 ml of dry THF at room temperature over 5 min. The mixture was stirred at room temperature for 11.5 hours. After adding water, the mixture was extracted with

ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: n-hexane:ethyl acetate=1:1) to give 4.01 g of tert-butyl (pyridin-3-yl)methoxyacetate (Yield: 56.3%) as a dark brown oil.

5

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.42(3H, d, J=7.3 Hz), 1.50(9H, s), 3.96(1H, q, J=6.6 Hz), 4.47, 4.69 (2H, ABq, J=11.0 Hz), 7.29(1H, dd, J=5.1, 8.1 Hz), 7.75(1H, d, J=8.1 Hz), 8.5(1H, d, J=4.4 Hz), 8.60(1H, s)

- 10 (131-2) To a solution of 1.09 g of the compound from the process (131-1) (4.59 mmol) in 5 ml of dichloromethane was added 8 ml of trifluoroacetic acid, and the solution was stirred at room temperature for 9.5 hours. After evaporation, to the residue was added 25 ml of dichloromethane and 3 ml of pyridine. Under ice-cooling, to the solution was added dropwise 0.70 g of 2-chloro-1,3-
- 15 dimethylimidazolidinium chloride (4.1 mmol) in 8 ml of dichloromethane, and then the mixture was stirred for 30 min. To the solution was slowly added dropwise 0.98 g of the compound from Example 100, the process (100-2) (3.0 mmol) in 20 ml of dichloromethane and 10 ml of pyridine under ice-cooling over 15 min, and the solution was warmed to room temperature with stirring for 8 hours. After
- 20 adding saturated sodium bicarbonate aq., the mixture was diluted with water and extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:methanol=8:1) to give 1.19 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-[N-[2-(pyridin-3-yl)methoxypropyl]amino]benzamide as a 2:3 (molar ratio) mixture with 1,3-dimethyl-2-imidazolinone.
- 25

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.51(9H, s), 1.54(3H, d, J=6.6 Hz), 4.13(4H, q, J=6.6 Hz), 4.65, 4.71(2H, ABq, J=11.7 Hz), 7.12-7.18(2H, m), 7.28-7.37(3H, m), 7.65(2H, d, J=8.1 Hz), 7.73(2H, br.d, J=5.9 Hz), 7.96(2H, d, J=8.8 Hz), 8.59-8.64(3H, m), 9.39(1H, br.s)

30

(131-3) To a solution of 1.19 g of the compound from the process (131-2) (1.8 mmol) in 10 ml of dichloromethane was added 20 ml of 15% (vol/vol) trifluoroacetic acid in dichloromethane, and the solution was stirred at room temperature for 4.5 hours. The solution was poured into saturated sodium bicarbonate, and dichloromethane was removed by evaporation. The resulting aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue were added methanol and diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 585 mg of N-(2-aminophenyl)-4-[N-[2-(pyridin-3-yl)methoxypropionyl]amino]benzamide as a light brown solid.

mp: 144-148°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.40(3H, d, J=6.6 Hz), 4.14(1H, q, J=6.6 Hz), 4.56 and 4.65(2H, ABq, J=11.8 Hz), 4.89(2H, br.s), 6.60(1 H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.40(1H, dd, J=4.4 Hz, 7.3 Hz), 7.78-7.85(3H, m), 7.97(2H, d, J=8.8 Hz), 8.52(1H, dd, J=1.5, 5.1 Hz), 8.61(1H, d, J=2.1 Hz), 9.60(1H, s), 10.15(1H, s)

Example 132

Preparation of N-(2-aminophenyl)-4-(N-benzylamino)carbonylbenzamide (Table 1: Compound 8)

(132-1) To a suspension of 13.0 g of monomethyl terephthalate (72.2 mmol) in 100 ml of toluene was added dropwise 10 ml of thionyl chloride at room temperature. After stirring at 80°C for 3 hours, the solvent and an excess amount of thionyl chloride were removed by evaporation. The residue was suspended in 100 ml of dioxane, and 9.98 g of 2-nitroaniline (72.2 mmol) were added to the suspension, followed by refluxing with heating for 4 hours.

After cooling and evaporation, the residue was washed with methanol to give 20.3 g of N-(2-nitrophenyl)-4-methoxycarbonylbenzamide (Yield: 93.7%) as a yellow solid.

5

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.91(3H, s), 7.43-7.49(1H, m), 7.76-7.78(2H, m), 8.03(1H, d, J=8.1 Hz), 8.08(2H, d, J=8.8 Hz), 8.14(2H, d, J=8.8 Hz), 10.94(1H, s)

- 10 (132-2) To a solution of 4.24 g of the compound from the process (132-1) in 50 ml of THF and 50 ml of methanol was added 0.4 g of 10% Pd/C in a stream of nitrogen, and the mixture was stirred in a stream of hydrogen for 1.5 hours. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was washed with methanol to give 3.4 g of N(2-aminophenyl)-4-
- 15 methoxycarbonylbenzamide (Yield: 87.5%) as a light yellow solid.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.90(3H, s), 4.95(2H, s), 6.60(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=7.3 Hz), 6.99(1H, dd, J=7.3, 7.3 Hz), 7.17(1H, d, J=7.3 Hz), 8.08(2H, d, J=8.1 Hz), 8.11(2H, d, J=8.1 Hz), 9.85(1H, s)

20

- (132-3) To a solution of 2.71 g of the compound from the process (132-2) (10.0 mmol) in 100 ml of dioxane and 50 ml of water was added 5% sodium hydroxide aq. under ice-cooling, and then were added dropwise 2.62 g of di-tert-butyl dicarbonate (12.0 mmol) in 40 ml of dioxane. The mixture was stirred
- 25 at room temperature for 4 hours and left overnight. To the mixture were added saturated brine and ethyl acetate, and the two layers were separated. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with methanol to give 3.54 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-
- 30 methoxycarbonylbenzamide (Yield: 95.7%) as a light brown solid.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.44(9H, s), 3.90(3H, s), 7.12-

7.24(2H, m), 7.55-7.58(2H, m), 8.09(2H, d, J=8.8 Hz), 8.10(2H, d, J=8.8 Hz),
8.72(1H, s), 10.00(1H, s)

(132-4) A suspension of 3.00 g of the compound from the process (132-3) (8.10
5 mmol) in 50 ml of methanol and 25 ml of 0.5N lithium hydroxide aq. was heated
with stirring at 40°C for 5 hours. After removing methanol by evaporation, to the
residue was added 1N hydrochloric acid, and the mixture was extracted with
ethyl acetate. The organic layer was washed with a small amount of water and
saturated brine, dried and evaporated. The residue was washed with methanol
10 to give 2.24 g of terephthalic mono-2-(N-tert-butoxycarbonyl)aminoanilide
(Yield: 77.6%) as a light brown solid.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.45(9H, s), 7.12-7.21(2H, m), 7.53-
7.58(2H, m), 8.06(2H, d, J=8.8 Hz), 8.10(2H, d, J=8.8 Hz), 8.71(1H, s), 9.97(1H,
15 s)

(132-5) To a suspension of 0.20 g of the compound from the process (132-4)
(0.56 mmol) in 4 ml of dichloromethane were added 0.14 g of benzylamine (1.3
mmol) and then 0.21 ml of triethylamine (1.5 mmol). To the solution was added
20 0.25 g of 2-chloro-1,3-dimethylimidazolium chloride (1.48 mmol) under ice-
cooling, and then the mixture was stirred under ice-cooling for an hour and at
room temperature for an hour. After diluting with chloroform and adding water,
the aqueous layer was extracted with chloroform.

25 The combined organic layer was washed with saturated brine, dried and
evaporated. The residue was purified by column chromatography on silica gel
(eluent: chloroform:methanol=10:1). The solid obtained was washed with diethyl
ether to give 279 mg of N-(2-tert-butoxycarbonylamino)phenyl)-4-(N-
30 benzylamino)carbonylbenzamide (Yield: 62.6%) as a white solid.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.45(9H, s), 4.52(2H, d, J=5.8 Hz),

7.13-7.28 (4H, m), 7.34-7.35(3H, m), 7.56(2H, d, J=8.1 Hz), 8.05(4H, s),
8.71(1H, br.s), 9.23(1H, t), 9.94(1H, s)

(132-6) To 151 mg of the compound from the process (132-5) (0.339 mmol) was
5 added 5 ml of 4N hydrochloric acid-dioxane at room temperature, and the
mixture was stirred for 4 hours. After evaporation, the mixture was partitioned
between ethyl acetate and saturated sodium bicarbonate aq. After removing the
precipitate, the aqueous layer was extracted with ethyl acetate. The combined
organic layer was washed with saturated brine, dried and evaporated. To the
10 residue was added diethyl ether, and the precipitate was collected by filtration
and dried to give 78 mg of N-(2-aminophenyl)-4-(N-
benzylamino)carbonylbenzamide (Yield: 67%) as a white solid.

mp: 239-241°C(dec.)

15 ¹ H NMR(270 MHz, DMSO-d6) .delta. ppm: 4.51(2H, s), 4.93(2H, br.d), 6.60(1H,
dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.95(1H, dd, J=7.3, 8.3 Hz), 7.18(1H,
d), 7.23-7.35(5H, m), 8.01(2H, d, J=8.8 Hz), 8.07(2H, d, J=8.8 Hz), 9.22(1H,
br.t), 9.81(1H, br.s)

20 As described in Example 132, the compound of Example 133 was prepared,
whose melting point (mp), ¹ H NMR data and IR data are shown below.

25 Example 133

N-(2-aminophenyl)-4-[N-(2-phenylethyl)amino]carbonylbenzamide (Table 1:
Compound 9)

30 mp: 237-240°C(dec.)

¹ H NMR(270 MHz, DMSO-d6) .delta. ppm: 2.87(2H, t, J=7.3 Hz), 3.51(2H, dt,

J=5.9, 7.3 Hz), 4.94(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.98(1H, dd, J=7.3, 7.3 Hz), 7.15-7.34(6H, m), 7.93(2H, d, J=8.1 Hz), 8.04(2H, d, J=8.1 Hz), 8.73(1H, t, J=5.1 Hz), 9.76(1H, br.s)

5 IR(KBr)cm⁻¹ : 3396, 3320, 1625, 1602, 1539, 1458, 1313, 699

Example 134

10 Preparation of N-(2-aminophenyl)-4-[N-(4-nitrophenoxyacetyl)amino]benzamide
(Table 1: Compound 54)

(134-1) To a solution of 3 g of the compound from Example 100, the process
(100-2) (9.2 mmol) and 2.16 g of 4-nitrophenoxyacetic acid (11.0 mmol) in 7 ml
15 of DMF were added 2.82 g of dicyclohexylcarbodiimide (13.8 mmol) in 5 ml of
DMF and a catalytic amount of N,N-dimethylaminopyridine, and the mixture was
stirred for one day. After completion of the reaction, ethyl acetate was added to
the mixture, insolubles were filtered off through celite, and the solvent was
removed by evaporation.

20

The residue was recrystallized from chloroform to give 2.34 g of N-[2-(tert-
butoxycarbonylamino)phenyl]-4-[(4-nitrophenoxyacetyl)amino]benz amide
(Yield: 50%).

25 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.45(9H, s), 4.97(2H, s), 7.12-
7.26(3H, m), 7.23(2H, d, J=8.8 Hz), 7.53(1H, dt, J=2.2, 7.3 Hz), 7.79(2H, d,
J=8.8 Hz), 7.95(2H, d, J=8.8 Hz), 8.25(2H, d, J=8.8 Hz), 8.71(1H, s), 9.79(1H,
s), 10.52(1H, s)

30 (134-2) To a solution of 0.7 g of the compound from the process (134-1) (1.38
mmol) in 10 ml of acetonitrile was added 1.26 ml of iodotrimethylsilane (8.85
mmol) at room temperature, and the solution was stirred for 2 hours. After

completion of the reaction, the solution was concentrated. Ethyl acetate was added to the residue, the solution was stirred for 20 min, and the precipitated crystals were collected by filtration. The crystals were dissolved in methyl ethyl ketone. The solution was washed with saturated sodium thiosulfate aq. and saturated brine in sequence, dried over anhydrous magnesium sulfate, and evaporated. The residue was washed with ethyl acetate to give 0.22 g of N-(2-aminophenyl)-4-[N-(4-nitrophenoxyacetyl)amino]benzamide (Yield: 39%) as white crystals.

mp: 212-215°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.97(2H, s), 6.88(1H, t, J=7.3 Hz), 6.99(1H, d, J=7.3 Hz), 7.11(1H, t, J=7.3 Hz), 7.23(2H, d, J=8.8 Hz), 7.24(1H, m), 7.77(2H, d, J=8.8 Hz), 8.00(2H, d, J=8.8 Hz), 8.25(2H, d, J=8.8 Hz), 9.89(1H, s), 10.52(1H, s)

IR(KBr)cm⁻¹ : 3382, 3109, 1650, 1591, 1508, 1341

Example 135

Preparation of N-(2-aminophenyl)-4-[(4-aminophenoxyacetyl)amino]benzamide (Table 1: Compound 55)

To a solution of 1.41 g of the compound from Example 134, the process (134-1) (2.78 mmol) in 15 ml of methanol and 25 ml of THF was added 10% Pd-C, and the mixture was stirred in an atmosphere of hydrogen, at room temperature for an hour. After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated. The residue was triturated with diisopropyl ether to give 1.1 g of N-[2-(tert-butoxycarbonylamino)phenyl]-4-[(4-aminophenoxyacetyl)amino]benz amide.

The product was dissolved in 15 ml of acetonitrile. To the solution was added 0.74 ml of iodotrimethylsilane (5.20 mmol), and the mixture was stirred at room temperature for 3 hours. After completion of the reaction, the mixture was evaporated. The residue was washed with methyl ethyl ketone to give 0.86 g of
5 N-(2-aminophenyl)-4-[(4-aminophenoxyacetyl)amino]benzamide (Yield: 83%).

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.82(2H, s), 7.13(2H, d, J=8.8 Hz),
10 7.30-7.48(6H, m), 7.82(2H, d, J=8.8 Hz), 8.03(2H, d, J=8.8 Hz), 10.34(1H, s),
10.46(1H, s)

IR(KBr)cm⁻¹ : 2873, 2590, 1680, 1602, 1505, 1243

15

Example 136

Preparation of N-(2-aminophenyl)-4-(5-phenoxyethyl-1,3-oxazolin-2-on-3-yl)benzamide (Table 2: Compound 1)

20

(136-1) To 0.7 g of tert-butyl 4-(N-benzyloxycarbonylamino)benzoate (2.14 mmol) in 10 ml of THF at -78°C was added dropwise 1.33 ml of n-butyl lithium (2.25 mmol) over 5 min. The mixture was stirred at the same temperature for 1.5 hours. To the mixture was then added 0.31 ml of phenylglycidol (2.29
25 mmol), and the reaction mixture was then stirred at the same temperature for an hour and left overnight at room temperature. After adding saturated ammonium chloride aq., the mixture was extracted twice with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from diethyl ether to give 0.31 g of N-[4-(tert-butoxycarbonyl)phenyl]-5-phenoxyethyl-1,3-oxazolin-2-one (Yield: 39%).
30

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.53(9H, s), 3.97(1H, dd, J=6.0, 8.8

Hz), 4.23-4.34(3H, m), 5.11(1H, m), 6.94-7.00(3H, m), 7.31(2H, m), 7.71(2H, d, J=8.8 Hz), 7.93(2H, d, J=8.8 Hz)

(136-2) To a solution of 0.26 g of the compound from the process (136-1) (0.704 mmol) in 4 ml of acetonitrile was added 0.15 ml of trimethylsilyl iodide (1.05 mmol), and the solution was stirred at room temperature for 2 hours. After completion of the reaction, the solution was concentrated. The concentrate was triturated with ethyl acetate-methyl ethyl ketone to give 0.2 g of N-(4-carboxyphenyl)-5-phenoxyethyl-1,3-oxazolin-2-one (Yield: 91%).

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.98(1H, dd, J=6.6, 9.6 Hz), 4.23-4.34(3H, m), 5.10(1H, m), 6.94-6.99(3H, m), 7.30(2H, t, J=8.1 Hz), 7.72(2H, d, J=8.8 Hz), 7.98(2H, d, J=8.8 Hz), 12.85(1H, s)

(136-3) To a solution of 0.15 g of the compound from the process (136-2) (0.479 mmol) in 7 ml of dichloromethane were added a catalytic amount of DMF and 0.12 ml of oxalyl chloride (1.40 mmol), and the solution was stirred at room temperature for 2 hours. The solution was concentrated and the residual solvent was azeotropically removed twice with toluene. To a solution of the residue in 4 ml of dichloromethane were added a solution of 0.105 g of the compound from Example 1, the process (1-2) (0.504 mmol) and 0.12 g of pyridine (1.52 mmol) in 1 ml of dichloromethane under ice-cooling, and the solution was warmed to room temperature and stirred for an hour. After completion of the reaction, water was added. The mixture was extracted twice with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated. The residue was triturated with diisopropyl ether to give 0.25 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-(5-phenoxyethyl-1,3-oxazolin-2-on-3-yl)benzamide (Yield: quantitative).

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 1.52(9H, s), 4.11(1H, dd, J=5.9, 6.6 Hz), 4.21-4.27(3H, m), 5.01(1H, m), 6.84(1H, br.s), 6.91(2H, d, J=8.8 Hz), 7.01(1H, t, J=7.4 Hz), 7.12-7.34(5H, m), 7.68(2H, d, J=8.8 Hz)

(136-4) To a solution of 0.22 g of the compound from the process (136-3) (0.437 mmol) in 4 ml of acetonitrile was added 0.1 ml of trimethylsilyl iodide (0.703 mmol) at room temperature, and the solution was stirred for 2 hours. After
5 adding saturated sodium thiosulfate aq., the mixture was extracted twice with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from methanol to give 0.13 g of N-(2-aminophenyl)-4-(5-phenoxyethyl-1,3-oxazolin-2-on-3yl)benzamide (Yield: 74%) as white crystals.

10

mp: 165-170°C(dec.)

¹ H NMR(270 MHz, DMSO-d6) .delta. ppm: 4.01(1H, dd, J=6.6, 9.6 Hz), 4.28-4.34(3H, m), 5.12(1H, m), 5.23(2H, br.s), 6.64(1H, t, J=7.4 Hz), 6.81(1H, d, J=8.1 Hz), 6.95-7.00(3H, m), 7.18(1H, d, J=6.6 Hz), 7.31(2H, t, J=8.1 Hz),
15 7.72(2H, d, J=8.8 Hz), 8.05(2H, d, J=8.8 Hz), 9.69(1H, s)

IR(KBr)cm-1 : 3393, 1740, 1610, 1508, 1253

20 As described in Example 136, the compounds of Examples 137 to 143 were prepared, each of whose melting point (mp), ¹ H NMR data and/or IR data are shown below.

25 Example 137

N-(2-aminophenyl)-4-[5-(4-nitrophenoxy)methyl-1,3-oxazolin-2-on-3-yl]benzamide (Table 2: Compound 2)

30 mp: 162-164°C

¹ H NMR(270 MHz, DMSO-d6) .delta. ppm: 3.97(1H, dd, J=6.6, 9.5 Hz),

4.10(1H, dd, J=5.1, 11.0 Hz), 4.17(1H, dd, J=3.7, 11.0 Hz), 4.27(1H, t, J=8.8 Hz), 6.53-6.80(6H, m), 6.97(1H, t, J=8.1 Hz), 7.16(1H, d, J=6.6 Hz), 7.72(2H, d, J=8.8 Hz), 8.04(2H, d, J=8.8 Hz), 9.65(1H, s)

5 IR(KBr)cm⁻¹ : 3356, 2365, 1741, 1609, 1510, 1247

Example 138

10 N-(2-aminophenyl)-4-(5-benzyloxymethyl-1,3-oxazolin-2-on-3-yl)benzamide hydrochloride (Table 2: hydrochloride of Compound 3)

mp: 181-183°C

15 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.69(1H, dd, J=5.2, 11.0 Hz), 3.76(1H, dd, J=3.7, 11.0 Hz), 3.91(1H, dd, J=5.9, 8.8 Hz), 4.59(2H, s), 4.93(1H, m), 7.26-7.41(8H, m), 7.51(1H, m), 7.74(2H, d, J=8.8 Hz), 8.15(2H, d, J=8.8 Hz), 10.42(1H, s)

20

Example 139

N-(2-aminophenyl)-4-[5-(pyridin-3-yl)oxymethyl-1,3-oxazolin-2-on-3-yl]benzamide (Table 2: Compound 4)

25

mp: 199-201°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.01(1H, dd, J=6.6, 8.8 Hz), 4.28-4.46(3H, m), 4.96(2H, br.s), 5.14(1H, m), 6.61(1H, t, J=7.4 Hz), 6.79(1H, d, J=7.4 Hz) 6.98(1H, t, J=7.4 Hz), 7.16(1H, d, J=7.4 Hz), 7.36(1H, dd, J=4.4, 8.1 Hz), 7.44(1H, dd, J=1.5, 8.1 Hz)

30

IR(KBr)cm⁻¹ : 2815, 2631, 2365, 1752, 1610, 1520, 1225

Example 140

5

N-(2-aminophenyl)-4-[5-(pyridin-3-yl)methyloxymethyl-1,3-oxazolin-2-on-3-yl]benzamide (Table 2: Compound 5)

mp: 160-164°C(dec.)

10

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.73(1H, dd, J=5.2, 11.7 Hz), 3.79(1H, dd, J=2.9, 11.7 Hz), 3.91(1H, dd, J=5.9, 8.8 Hz), 4.21(1H, t, J=8.8 Hz), 4.62(2H, s), 4.91(3H, br.s), 6.60(1H, t, J=7.4 Hz), 6.78(1H, d, J=7.4 Hz), 6.98(1H, t, J=7.4 Hz), 7.16(1H, d, J=7.4 Hz), 7.38(1H, dd, J=4.4, 7.4 Hz), 7.69(2H, d, J=8.8 Hz), 7.71(1H, m), 8.03(2H, d, J=8.8 Hz), 8.51(1H, dd, J=1.5, 4.4 Hz), 8.54(1H, d, J=1.5 Hz), 9.65(1H, s)

15

IR(KBr)cm⁻¹ : 3368, 1742, 1648, 1608, 1492, 1226

20

Example 141

N-(2-aminophenyl)-4-[5-(3-nitrophenoxy)methyl-1,3-oxazolin-2-on-3-yl]benzamide (Table 2: Compound 6)

25

mp: 230°C(dec.)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.04(1H, t, J=8.8 Hz), 4.32(1H, t, J=8.8 Hz), 4.41-4.53(2H, m), 4.91(2H, s), 5.15(1H, m), 6.61(1H, t, J=7.4 Hz), 6.79(1H, d, J=7.4 Hz), 6.98(1H, t, J=7.4 Hz), 7.16(1H, d, J=7.4 Hz), 7.46(1H, dd, J=1.5, 8.1 Hz), 7.61(1H, t, J=8.1 Hz), 7.71-7.79(3H, m), 7.87(1H, d, J=8.1 Hz), 8.06(2H, d, J=8.8 Hz), 9.66(1H, s)

30

IR(KBr)cm⁻¹ : 3363, 3095, 2365, 1741, 1608, 1529

5 Example 142

N-(2-aminophenyl)-4-[5-(pyridin-2-yl)methyloxymethyl-1,3-oxazolin-2-on-3-yl]
]benzamide (Table 2: Compound 7)

10 mp: 172-174°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.79(1H, dd, J=5.2, 11.0 Hz),
3.85(1H, dd, J=2.9, 11.0 Hz), 3.95(1H, dd, J=6.6, 9.6 Hz), 4.23(1H, t, J=9.6 Hz),
4.67(2H, s), 4.90(2H, s), 4.95(1H, m), 6.60(1H, t, J=7.4 Hz), 6.78(1H, d, J=7.4
15 Hz), 6.97(1H, t, J=7.4 Hz), 7.16(1H, d, J=7.4 Hz), 7.29(1H, dd, J=5.2, 6.6 Hz),
7.40(1H, d, J=6.6 Hz), 7.70(2H, d, J=8.8 Hz), 7.78(1H, dt, J=2.2, 7.4 Hz),
8.03(2H, d, J=8.8 Hz), 8.51(1H, d, J=4.4 Hz), 9.64(1H, s)

IR(KBr)cm⁻¹ : 3369, 1743, 1651, 1608, 1492, 1283
20

Example 143

N-(2-aminophenyl)-4-[5-(pyridin-2-yl)oxymethyl-1,3-oxazolin-2-on-3-yl]benza
25 mide (Table 2: Compound 8)

mp: (amorphous)

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.96(1H, dd, J=5.9, 9.6 Hz), 4.21-
30 4.40(3H, m), 4.90(2H, s), 5.03(1H, m), 6.28(1H, t, J=6.6 Hz), 6.43(1H, d, J=9.6
Hz), 6.60(1H, t, J=6.6 Hz), 6.78(1H, d, J=6.6 Hz), 6.97(1H, t, J=7.4 Hz),
7.15(1H, d, J=6.6 Hz), 7.46(1H, dt, J=7.4, 1.5 Hz), 7.67(2H, d, J=8.8 Hz),

7.69(1H, m), 8.03(2H, d, J=8.8 Hz), 9.64(1H, s)

Example 144

5

N-(2-aminophenyl)-4-[N-{3-[(pyridin-3-yl)methylamino]cyclobuten-1,2-dion-4-yl}aminomethyl]benzamide (Table 2: Compound 9)

(144-1) To a solution of 0.073 g of 3,4-di-n-butoxy-3-cyclobuten-1,2-dione
10 (0.323 mmol) in 2 ml of THF was added 0.1 g of the compound from Example 1,
the process (1-4) (0.293 mmol), and the solution was stirred for 4 hours. After
adding 0.033 ml of 3-aminomethylpyridine (0.327 mmol), the solution was
reacted for a day. After completion of the reaction, water was added to the
solution, and the mixture was extracted twice with methyl ethyl ketone. The
15 organic layer was dried over anhydrous magnesium sulfate and evaporated.
The residue was triturated with methanol to give 0.12 g of N-[2-(N-tert-
butoxycarbonylamino)phenyl]-4-[N-{3-[(pyridin-3-yl)methylamin o]cyclobuten-
1,2-dion-4-yl}aminomethyl]benzamide (Yield: 78%)

20 ¹ H NMR(270 MHz, DMSO-d6) .delta. ppm: 1.44(9H, s), 4.75-4.81(4H, m),
7.15(1H, dt, J=2.2, 7.4 Hz), 7.20(1H, dt, J=2.2, 7.4 Hz), 7.40(1H, dd, J=2.2, 7.4
Hz), 7.47(2H, d, J=8.1 Hz), 7.54(2H, dd, J=2.2, 7.4 Hz), 7.73(1H, m), 7.94(2H,
d, J=8.1 Hz), 8.50(1H, m), 8.55(1H, d, J=1.5 Hz), 8.67(1H, s), 9.82(1H, s)

25 (144-2) To a solution of 0.1 g of the compound from the process (144-1) (0.19
mmol) in 4 ml of dioxane and 1 ml of methanol was added 4 ml of 4N
hydrochloric acid-dioxane, and the mixture was reacted for 2 hours. After
completion of the reaction, the mixture was concentrated and neutralized with
saturated sodium bicarbonate aq. Methyl ethyl ketone was added to the
30 mixture, and the precipitated crystals were collected by filtration to give 0.04 g of
N-(2-aminophenyl)-4-[N-{3-[(pyridin-3-yl)methylamino]cyclobuten-1,2-dion-4 -
yl}aminomethyl]benzamide (Yield: 49%).

mp: 230°C

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.76(2H, s), 4.79(2H, s), 4.90(2H, s), 6.60(1H, t, J=7.4 Hz), 6.78(1H, d, J=7.4 Hz), 6.97(1H, t, J=7.4 Hz), 7.16(1H, d, J=7.4 Hz), 7.39(1H, m), 7.43(2H, d, J=8.1 Hz), 7.73(1H, d, J=8.1 Hz), 7.97(2H, d, J=8.1 Hz), 7.99(1H, br.s), 8.51(1H, d, J=8.1 Hz), 8.55(1H, s), 9.64(1H, s)

Example 145

N-(2-aminophenyl)-4-[3-(pyridin-3-yl)methylimidazolin-2-on-1-yl]methylbenzamide (Table 2: Compound 10)

(145-1) Potassium carbonate (7.88 g; 57 mmol) was added to a solution of 4.92 g of ethylene urea (57 mmol), 5.73 g of methyl 4-bromomethylbenzoate (25 mmol) and 1.85 g of tetra-n-butylammonium iodide (5.0 mmol) in 30 ml of DMF, and the mixture was heated with stirring at 80°C for 5 hours. After cooling, the solid was collected by filtration and washed with ethyl acetate. The filtrate was concentrated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:methanol=10:1). To the light yellow oil obtained was added diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 3.36 g of N-(4-methoxycarbonylphenylmethyl)imidazolin-2-one (Yield: 57.4%) as a light brown solid.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 3.28-3.35(2H, m), 3.41-3.47(2H, m), 3.92(3H, s), 4.42(2H, s), 4.61(1H, br.s), 7.35(2H, d, J=8.1 Hz), 8.01(2H, d, J=8.1 Hz)

(145-2) Saturated sodium bicarbonate aq. was added to 2.05 g of 3-chloromethylpyridine hydrochloride (12.5 mmol), and the mixture was extracted

with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residual solvent was azeotropically removed from the residue with toluene. To the residue was added 5 ml of DMF and then 0.37 g of tetra-n-butylammonium iodide (1.0 mmol) to prepare a solution of a benzyl
5 halide in DMF. To a suspension of 0.30 g of sodium hydride (60% oil dispersion) (7.5 mmol) in 5 ml of DMF was slowly added dropwise a solution of 1.17 g of the compound from the process (145-1) (5.0 mmol) in 10 ml of DMF, and the solution was stirred at room temperature for 30 min. After adding the above solution of the benzyl halide, the resulting solution was heated with stirring at
10 80°C for 7 hours, and then left at room temperature overnight. After removing DMF, the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate-methyl ethyl ketone (2:1). The combined organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent:ethyl
15 acetate:methanol=10:1) to give 1.17 g of N-(4-methoxycarbonylphenylmethyl)-N'-(pyridin-3-yl)methylimidazolin-2-one (Yield: 72.3%) as a brown oil.

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 3.20(4H, s), 3.92(3H, s), 4.44(2H, S), 4.46(2H, S), 7.27-7.36(3H, m), 7.64-7.69(1H, m), 8.01(2H, d, J=8.1 Hz),
20 8.53-8.56(2H, m)

(145-3) To a solution of 0.55 g of the compound from the process (145-2) (1.7 mmol) in 8 ml of methanol and 8 ml of water were added 110 mg of lithium hydroxide monohydrate (1.7 mmol) at room temperature, and the solution was
25 heated with stirring at 50°C for 1.5 hours. Additional lithium hydroxide monohydrate (0.05 g; 1.2 mmol) was added, and the solution was stirred at 50°C for additional 1.5 hours. The solution was acidified to pH 3-4) with 10% hydrochloric acid. Saturated brine was added, and the mixture was extracted twice with ethyl acetate and once with ethyl acetate-methyl ethyl ketone (1:1).
30 The organic layer was dried over anhydrous sodium sulfate and evaporated. The residue was dried to give 0.32 g of 4-[3-(pyridin-3-yl)methylimidazolin-2-on-1-yl]methylbenzoic acid (Yield: 61%) as a brown oil.

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.17(2H, s), 3.20(2H, s), 4.36(2H, s), 4.38(2H, s), 7.35-7.42(3H, m), 7.68(1H, dd, J=6.6 Hz), 7.92(2H, d, J=8.1 Hz), 8.51(2H, m)

5

(145-4) To a solution of 0.31 g of the compound from the process (145-3) (1.0 mmol) in 12 ml of dichloromethane was added dropwise 0.3 ml of oxalyl chloride (3.5 mmol) at room temperature, and the solution was stirred at room temperature for 30 min and then at 40°C for 1.5 hours. After evaporation, the residual solvent was azeotropically removed with toluene, and the residue was suspended in 10 ml of dichloromethane. To the suspension under ice-cooling was added dropwise 0.21 g of the compound from Example 1, the process (1-2) (1.0 mmol) in 2 ml of dichloromethane and 2 ml of pyridine. The mixture was warmed with stirring to room temperature and left at room temperature overnight. After adding saturated sodium bicarbonate aq., the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent:ethyl acetate:methanol=20:1) to give 0.10 g of N-(2-tert-butoxycarbonylamino-phenyl)-4-[3-(pyridin-3-ylmethyl)imidazolin-2-on-1-yl]methylbenzamide (Yield: 20%) as a brown oil.

10

15

20

¹ H NMR(270 MHz, CDCl₃) .delta. ppm: 1.52(9H, s), 3.20(4H, s), 4.45(2H, s), 4.48(2H, s), 6.75(1H, br.s), 7.15-7.40(5H, m), 7.65-7.70(2H, m), 7.83(1H, d, J=7.3 Hz), 7.94(2H, d, J=8.1 Hz), 8.50-8.60(3H, br.m)

25

(145-5) To a solution of 100 mg of the compound from the process (145-4) (0.20 mmol) in 2 ml of dioxane was added 2 ml of 4N hydrochloric acid-dioxane and then 0.5 ml of methanol to make the mixture homogenous. After stirring for 2 hours, the solution was neutralized with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was dried under reduced pressure to give 47 mg of N-(2-aminophenyl)-4-[3-(pyridin-3-yl)methylimidazolin-2-on-1-

30

yl)methylbenz amide (Yield: 58%) as a brown oil.

mp: (amorphous)

5 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 3.20(4H, s), 4.37(2H, s), 4.39(2H, s), 4.87(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.35-7.41(3H, m), 7.68(1H, d, J=8.1 Hz), 7.90-8.00(2H, m), 8.50(2H, br.s), 9.63(1H, br.s)

10

Example 146

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide 0.5 fumarate (Table 1: fumarate of
15 Compound 82)

To 10 ml of methanol were added 310 mg of the compound from Example 48, and the mixture was heated to dissolve the solid. To the solution was added 96 mg of fumaric acid in methanol, and the solution was cooled. The precipitated
20 crystals were collected by filtration and recrystallized from 5 ml of methanol to give 200 mg of the desired product (Yield: 56%).

mp: 166-167°C

25 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.28(2H, d, J=6.6 Hz), 5.10(2H, s), 6.60(1H, t, J=8.0 Hz), 6.63(1H, s), 6.78(1H, d, J=8.0 Hz), 6.90-7.50(5H, m), 7.70-8.00(4H, m), 8.53(1H, d, J=3.6 Hz), 8.60(1H, s), 9.63(1H, s)

IR(KBr)cm⁻¹ : 3332, 1715, 1665, 1505, 1283, 1136, 1044, 983, 760, 712

30 Elementary analysis for C.sub.21 H.sub.20 N.sub.4 O.sub.3 +1/2C.sub.4 H.sub.4 O.sub.4

	C	H	N
Calculated:	63.59	5.10	12.90
Observed:	63.56	5.22	12.97

As described in Example 146, the compounds of Examples 147 to 149 are prepared, each of whose melting point (mp), ¹H NMR data, IR data and/or elementary analysis data are shown below.

Example 147

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide maleate (Table 1: maleate of Compound 82)

mp: 123-124°C

¹H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.28(2H, d, J=6.6 Hz), 5.11(2H, s), 6.24(2H, s), 6.66(1H, t, J=8.0 Hz), 6.83(1H, d, J=8.0 Hz), 6.90-8.00(9H, m), 8.56(1H, d, J=3.6 Hz), 8.62(1H, s), 9.69(1H, s)

IR(KBr)cm⁻¹ : 3298, 1719, 1546, 1365, 1313, 1250, 1194, 1149, 1044, 993, 862, 751
Elementary analysis for C₂₁H₂₀N₄O₃ + C₄H₄O₄ + 0.3 H₂O

	C	H	N
Calculated:	60.31	4.98	11.25
Observed:	60.52	5.12	11.03

Example 148

- 5 N-(2-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide hydrochloride (Table 1: hydrochloride of Compound 82)

mp: 140(dec.) °C

- 10 ¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.31(2H, d, J=5.8 Hz), 5.24(2H, s), 7.10-7.60(6H, m), 7.90-8.50(5H, m), 8.70-8.90(2H, m), 10.46(1H, s)

IR(KBr)cm⁻¹ : 2553, 1715, 1628, 1556, 1486, 1254, 1049, 778, 687

15

Example 149

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide 0.7 fumarate (Table 1: fumarate of Compound 61)

20

As described in Example 146, the title compound was prepared from the compound of Example 46.

mp: 154-155°C

25

¹ H NMR(270 MHz, DMSO-d₆) .delta. ppm: 4.42(2H, d, J=5.9 Hz), 4.69(1H, s), 6.60(1H, t, J=8.0 Hz), 6.63(0.7H, s) 6.78(1H, d, J=8.0 Hz), 6.90-7.50(6H, m), 7.93(2H, d, J=8.0 Hz), 8.20-8.40(2H, m), 8.82(1H, br.s), 9.63(1H, s)

- 30 IR(KBr)cm⁻¹ : 3324, 1709, 1631, 1521, 1457, 1428, 1260, 1064, 806, 698
Elementary analysis for C₂₁H₂₀N₄O₃ +0.7 C₄H₄O₄ +0.7 H₂O

	C	H	N
Calculated:	60.79	5.19	11.91
Observed:	60.95	5.20	11.75

5

Compounds described in WO 98/35958 (compound a) and compounds
 10 described in EP 0847992 (US 6,174,905) (compound b) are incorporated by
 reference.

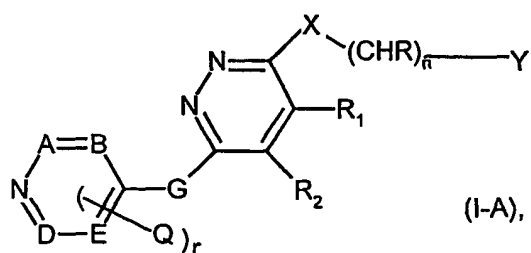
However, compounds described in WO 98/35958 (compound A) and
 compounds described in EP 0847992 (US 6,174,905) (compound B) show only
 15 minor effects on diseases if applied alone.

However, there is high demand for a medicament, or medicaments, which show
 a clear effect when applied to cancer or tumors, or diseases as discussed
 supra. Thus, there is a high demand for a medicament, such as a formulation or
 20 combination, respectively, which can overcome these problems.

It has now been found that a combination comprising

a) at least one compound from the group of compounds of formula I-A

25



30

wherein

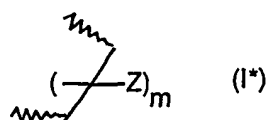
r is 0 to 2,

n is 0 to 2,

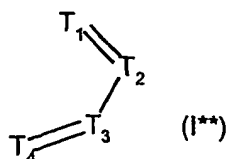
m is 0 to 4,

R₁ and R₂ (i) are lower alkyl or

5 (ii) together form a bridge in subformula I*



10 the binding being achieved via the two terminal carbon atoms, or
(iii) together form a bridge in subformula I**



15

wherein one or two of the ring members T₁, T₂, T₃ and T₄ can be nitrogen, and the others are in each case CH, and the binding is achieved via T₁ and T₄

20 A, B, D and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N;

G is lower alkylene, lower alkylene substituted by acyloxy or hydroxy, -CH₂-O-, CH₂-S-, -CH₂-NH-, oxa (-O-), thia (-S-), or imino (-NH-);

25

Q is lower alkyl;

R is H or lower alkyl;

30 X is imino, oxa, or thia;

Y is unsubstituted or substituted aryl, pyridyl, or cycloalkyl; and

Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N, N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or alkylphenylsulfinyl, substituents Z being the same or different from one another if more than 1 radical Z is present;

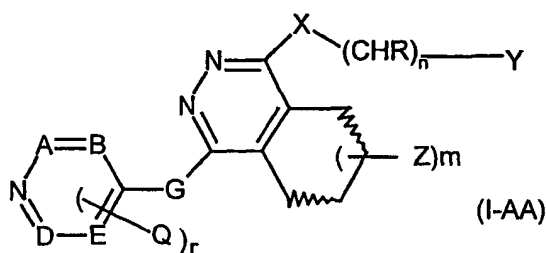
and wherein the bonds characterized, if present, by a wavy line are either single or double bonds;

or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom;

with the stipulation that, if Y is pyridyl or unsubstituted cycloalkyl, X is imino, and the remaining radicals are as defined, G is selected from the group comprising lower alkylene, $-\text{CH}_2\text{-O}-$, $-\text{CH}_2\text{-S}-$, oxa and thia; or a salt thereof;

or

at least one compound from the group of compounds of formula I-AA



wherein

r is 0 to 2,

n is 0 to 2,

m is 0 to 4,

A, B, D and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N;

5 G is lower alkylene, -CH₂-O-, -CH₂-S-, CH₂-NH-, oxa, thia, or imino;

Q is methyl;

R is H or lower alkyl;

10

X is imino, oxa, or thia;

Y is unsubstituted or substituted aryl, pyridyl, or cycloalkyl; and

15 Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or alkylphenylsulfinyl, substituents Z
20 being the same or different from one another if more than 1 radical Z is present;

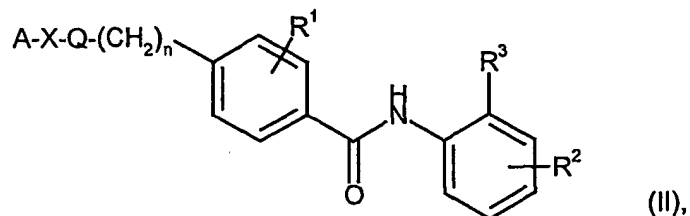
and wherein the bonds characterized by a wavy line are either single or double bonds;

25 or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom;

with the stipulation that, if Y is pyridyl or unsubstituted cycloalkyl, X is imino, and the remaining radicals are as defined, G is selected from the group comprising
30 lower alkylene, -CH₂-O-, -CH₂-S-, oxa and thia; or a salt thereof;

and

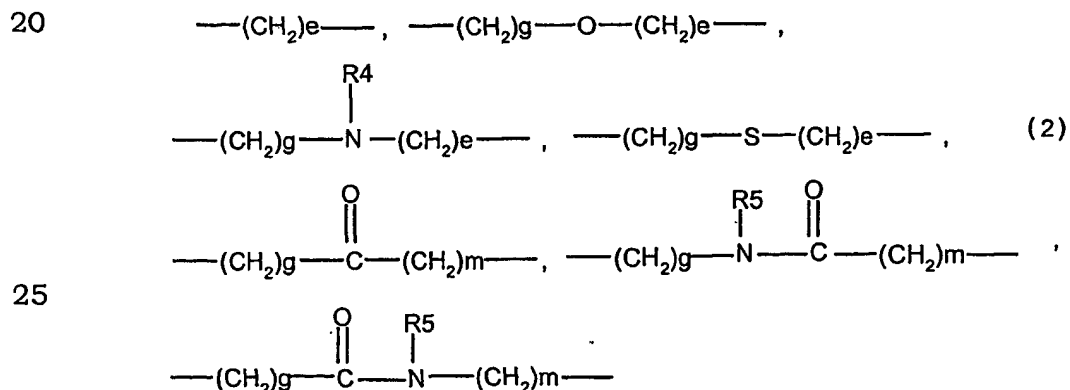
b) at least one compound from the group of compounds of formula II)



5 wherein

A is an optionally substituted phenyl group or an optionally substituted heterocyclic group wherein the substituent(s) for the phenyl group or the heterocyclic group is (are) 1 to 4 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;

X is a bond or a moiety having the following structure



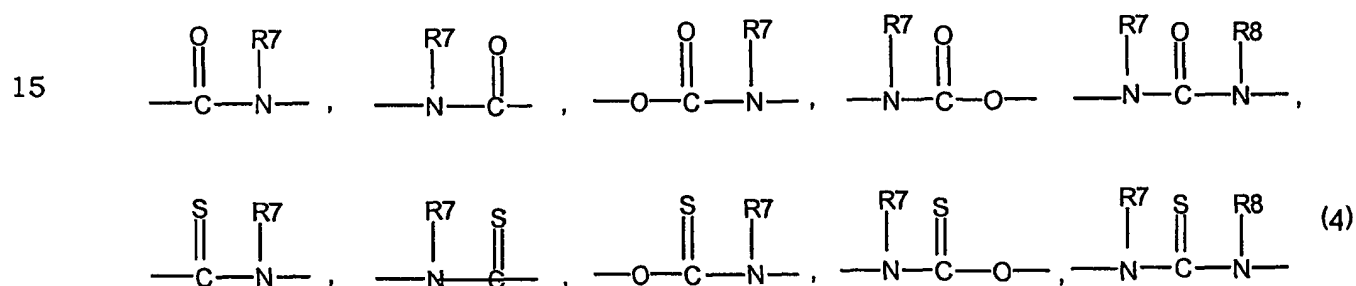
wherein e is an integer of 1 to 4; g and m are independently an integer of 0 to 4;
 R^4 is a hydrogen atom or an optionally substituted alkyl group having 1 to 4
 carbons, or the acyl group represented by formula (3)



wherein R^6 is an optionally substituted alkyl group having 1 to 4 carbons, a
 perfluoroalkyl group having 1 to 4 carbons, a phenyl group or a heterocyclic
 group; R^5 is a hydrogen atom or an optionally substituted alkyl group having 1
 10 to 4 carbons;

n is an integer of 0 to 4, provided that when X is a bond, n is not zero;

Q is a moiety having a structure selected from those illustrated in formula (4)



20 wherein R^7 and R^8 are independently hydrogen atom or an optionally
 substituted alkyl group having 1 to 4 carbons;

R^1 and R^2 are independently a hydrogen atom, a halogen atom, a hydroxyl
 group, an amino group, an alkyl group having 1 to 4 carbons, an alkoxy group
 25 having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an
 alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons,
 an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4
 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group
 having 1 to 4 carbons, a carboxyl group or an alkoxycarbonyl group having 1 to
 30 4 carbons;

R^3 is a hydroxyl or amino group or a pharmaceutically acceptable salt thereof,

will overcome the disadvantages of the known single compounds.

- 5 Especially it has been found, that a combination comprising
- a) at least one compound of general formula I-A) or formula I-AA)
and
 - b) at least one compound of general formula II)
and
 - 10 c) at least one anti-hormonal compound taken from the groups comprising
anti-oestrogen, anti-progesterone and anti-androgen compounds,
overcome the disadvantages of the known single compounds.

For example, the combination of compounds of general formula I-A or Formula
15 I-AA, and general formula II) together with the anti-hormonal compound
tamoxifen or derivatives thereof show a rapidly reduction of the tumor mass (s.
examples).

Beside tamoxifen other anti-hormonal compounds can also be used in
combination, such as for example onapristone or derivatives thereof, and
20 dihydrospirorenone or derivatives thereof.

Further, of selected interest as anti-hormonal compounds are the following
compounds:

- i) at least one anti-hormonal compound taken from the group of anti-
oestrogen compounds:
25 (Z)-2-[p-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethylamine
(tamoxifen),
1-[2-[4-(6-methoxy-2-phenyl-3,4-dihydro-1-naphthyl)phenoxy]ethyl]-
pyrrolidine hydrochloride (nafoxidine),
1-[p-(2-diethylaminoethoxy)phenyl]2-(p-methoxyphenyl)-1-
30 phenylethanol (Mer 25),
11 α -methoxy-17 α -ethynyl-1,3,5(10)-estratriene-3,17 β -diol,
16 β -ethylestradiol,

11-(3,17 β -dihydroxy-1,3,5(10)-estratrien-7 α -yl)undecanoic-acid(N-butyl-N-methyl)amide,

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl-[2-(piperidinyloxy)]phenyl]methanone,

- 5 ii) at least one anti-hormonal compound taken from the group of anti progesterone compounds

11 β -[(4-N,N-dimethylamino)phenyl]-17 β -hydroxy-17 α -propynyl-4,9(10) estradien-3-one,

- 10 11 β -[(4-N,N-dimethylamino)phenyl]-17 β -hydroxy-18-methyl-17 α -propynyl-4,9(10)-estradien-3-one,

11 β -[(4-N,N-dimethylamino)phenyl]-17 α β -hydroxy-17 α α -propynyl-D-homo-4,9(10)-16-estratrien-3-one,

11 β -p-methoxyphenyl-17 β -hydroxy-17 α -ethynyl-4,9(10)-estradien-3-one,

- 15 11 β -(4-dimethylaminophenyl)-17 α -hydroxy-17 β -(3-hydroxypropyl)-13-methyl-4,9-gonadien-3-one,

11 β -(4-dimethylaminophenyl)-17 α -hydroxy-17-(3-hydroxypropyl)-13 α -estra-4,9-dien-3-one (onapristone),

20 and

- iii) at least one anti-hormonal compound taken from the group of anti-androgen compounds:

6-chloro-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-dione,

- 25 6-chloro-17-hydroxypregna-4,6-diene-3,20-dione,

6-chloro-17-hydroxypregna-1,4,6-triene-3,20-dione,

6-chloro-3,17-dihydroxy-1 α ,2 α -methylenepregna-4,6-diene-20-one,

6-chloro-3-methoxy-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-20-one,

- 30 6-fluoro-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-dione,

17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-dione,

- 4,6-dichloro-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-dione,
 6-chloro-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-dione
 acetate (cyproterone acetat),
 6-chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate (chlormadione
 5 acetate),
 6-chloro-17 α β -acetoxy-17 α α -methyl-1 α ,2 α -methylene-D-homo-4,6-
 androstadiene-3,17-dione,
 6-chloro-17 α -acetoxy-17 β -methyl-1 α ,2 α -methylene-D-homo-4,6-
 androstadiene-3,17 α -dione,
 10 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-propionamide (flutamide),
 2-hydroxy-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-propionamide,
 2-methyl-4-[4-nitro-3-(trifluoromethyl)phenyl]-5,6-dihydro-2H-1,2,4-
 oxadiazin-3-one,
 6 β ,7 β ,15 β ,16 β -dimethylen-3-oxo-17 α -pregn-4-ene-21,17-carbolactone
 15 (dihydrospirorenone).

Of special interest are those combinations wherein a) comprises at least one
 compound from the group of compounds of formula I-A, wherein

- r is 0 to 2,
 20 n is 0 or 1,
 m is 0 or 1,
 A, B, D and E are in each case CH,
 G is lower alkylene, especially methylene,
 Q is methyl, which is bound to A, to D, or to A and D;
 25 R is H or lower alkyl,
 X is imino,
 Y is phenyl, which is unsubstituted or substituted by one or two substituents
 independently of one another from the group comprising amino; lower
 alkanoylamino; halogen; lower alkyl; halogen-lower alkyl; hydroxy; lower alkoxy;
 30 phenyl-lower alkoxy; cyano, or is pyridol;
 Z is amino; N-lower alkylamino; hydroxy-lower alkylamino; phenyl-lower

alkylamino; N, N-di-lower alkylamino; n-phenyl-lower alkyl-N-lower alkylamino; N,N-di-lower alkylphenylamino; lower alkanoylamino; or a substituent from the group comprising benzoylamino or phenyl-lower alkoxy-carbonylamino, wherein the phenyl radical in each case is unsubstituted or especially substituted by

5 nitro or amino, or by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy-carbonyl, lower alkanoyl or carbamoyl; or is halogen; and,

the bonds characterized by a wavy line are in each case a double bond or in each case a single bond;

10 or a salt thereof.

Of special interest are those combinations wherein a) comprises at least one compound from the group of compounds of formula I-A, wherein

r is 0 to 2,

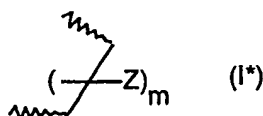
15 n is 0 or 1,

m is 0 or 1,

R₁ and R₂ (i) are lower alkyl or

(ii) together form a bridge in subformula I*

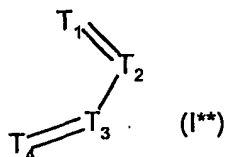
20



The binding being achieved via the two terminal carbon atoms, or

(iii) together form a bridge in subformula I**

25



wherein one of the ring members T₁, T₂, T₃ and T₄ can be nitrogen, and the

30 others are in each case CH, and the binding is achieved via T₁ and T₄

A, B, D and E are in each case CH, A, D and E are in each case CH and B is N;

G is lower alkylene, -CH₂-NH-, -CH₂-O-, hydroxymethylene, or benzoyloxymethylene,

5 Q is methyl, which is bound to A, to D, or to A and D;

R is H or lower alkyl,

X is imino, oxa, or thia,

10

Y is phenyl, which is unsubstituted or is substituted by one or two substituents independently of one another from the group comprising amino; lower alkanoylamino; halogen, lower alkyl; halogen-lower alkyl; hydroxy; lower alkoxy; phenyl-lower alkoxy; cyano; benzyloxy; lower alkenyl, C₈-C₁₂ alkoxy, lower
15 alkoxy carbonyl, carbamoyl lower alkyl carbamoyl, lower alkanoyl, phenyloxy, halogen-lower alkyloxy, lower alkoxy carbonyl, lower alkylmercapto, halogen-lower alkylmercapto, hydroxy-lower alkyl, lower alkylsulfonyl, halogen-lower alkylsulfonyl, phenylsulfonyl, dihydroxybora, 2-methylpyrimidin-4-yl, oxazol-5-yl, 2-methyl-1,3-dioxolan-2-yl, 1H-pyrazol-3-yl, 1-methylpyrazol-3-yl, and lower
20 alkylenedioxy bound to two adjacent C atoms, or is also pyridyl;

Z is amino; N-lower alkylamino; hydroxy-lower alkylamino; phenyl-lower alkylamino; N, N-di-lower alkylamino; n-phenyl-lower alkyl-N-lower alkylamino, N,N-di-lower alkylphenylamino; lower alkanoylamino; or a substituent from the
25 group comprising benzoylamino or phenyl-lower alkoxy carbonylamino, wherein the phenyl radical in each case is unsubstituted or substituted by nitro or amino, or by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, lower alkanoyl or carbamoyl; or is halogen; and,

30 if present (in formula IA), the bonds characterized by a wavy line are in each case a double bond or in each case a single bond; or a salt thereof.

Further, of special interest are those combinations wherein a) comprises at least one compound from the group of compounds of formula I-A, wherein r is 0,

- 5 n is 0 or 1,
m is 0;
A, B, D and E are in each case CH,
G is lower alkylene,
R is H;
10 X is imino,
Y is phenyl, which is unsubstituted or substituted by one or two substituents independently of one another from the group comprising amino; lower alkanoylamino; halogen; lower alkyl; halogen-lower alkyl; hydroxy; lower alkoxy; phenyl-lower alkoxy; and cyano; and
15 The bonds characterized by a wavy line are double bonds; or a salt thereof.

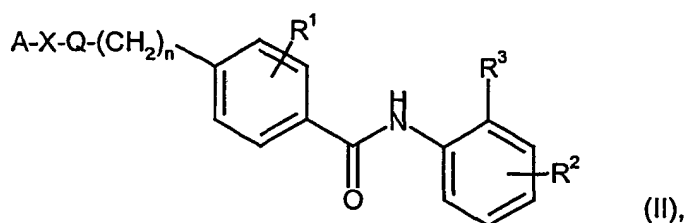
Of main interest are those combinations wherein a) comprises at least one compound from the group of compounds of formula I-A, wherein r is 0,

- 20 n is 0 or 1,
m is 0;
A, B D and E are in each case CH,
G is methylene,
R is H,
25 X is imino,
Y is phenyl, 2-, 3- or 4-aminophenyl, 2-, 3- or 4-acetylamino-phenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2,3-, 2,4-, 2,5- or 3,4-dichlorophenyl, chlorofluorophenyl, 2-, 3- or 4-methylphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4- hydroxyphenyl, 2-, 3- or 4- methoxycarbonyl,
30 methoxychlorophenyl, 2-, 3- or 4- benzyloxyphenyl, or 2-, 3- or 4-cyanophenyl;
and
the bonds characterized by the wavy line are double bonds; or a salt thereof.

Of most interest are those combinations wherein a) comprises at least one of the following selected compounds:

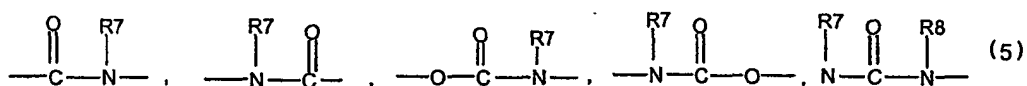
- 5 1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Methylanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Chloroanilino)-4-(4-pyridylmethyl)phthalazine;
1-Anilino-4-(4-pyridylmethyl)phthalazine;
1-Benzylamino-4-(4-pyridylmethyl)phthalazine;
- 10 1-(4-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Benzoyloxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(2-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Trifluoromethylanilino)-4-(4-pyridylmethyl)phthalazine;
- 15 1-(4-Fluoroanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Hydroxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Hydroxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Aminoanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3,4-Dichloroanilino)-4-(4-pyridylmethyl)phthalazine;
- 20 1-(4-Bromoanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Chloro-4-methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Cyanoanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Chloro-4-fluoroanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Methylanilino)-4-(4-pyridylmethyl)phthalazine;
- 25 or in each case a pharmaceutically acceptable salt thereof.

Of interest are those combinations wherein b) comprises at least one compound from the group of compounds of formula II), wherein n is an integer of 1 to 4.



Of special interest are those combinations wherein b) comprises at least one compound from the group of compounds of formula II), wherein n is an integer of 1 to 4.

Of further special interest are those combinations wherein b) comprises at least one compound from the group of compounds of general formula II), wherein Q is selected from the structures illustrated in formula (5):

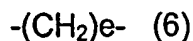


wherein R^7 and R^8 are as defined above.

Further of interest are those combinations wherein b) comprises at least one compound from the group of compounds of formula II), wherein A is an optionally substituted hetero ring, especially an optionally substituted pyridyl group.

Of special interest are also those combinations wherein b) comprises at least one compound from the group of compounds of formula II), wherein n is 1 to 4; Q is selected from the structures illustrated in formula (5); A is an optionally substituted hetero ring, especially optionally substituted pyridyl group; most preferred, wherein X is direct bond, most preferred wherein R^1 and R^2 are a hydrogen atom, most preferred, wherein R^3 is an amino group.

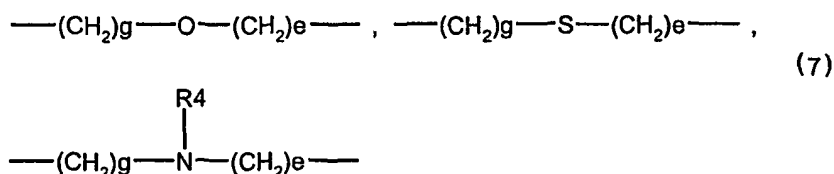
Also, of special interest are those combinations wherein b) comprises at least one compound from the group of compounds of formula II), wherein Q is selected from the structures illustrated in formula (5); A is an optionally substituted hetero ring, especially optionally substituted pyridyl group; most preferred, wherein X is the structure represented by formula (6):



wherein e is an integer of 1 to 4; most preferred wherein n is 1 and R¹ and R² are a hydrogen atom; most preferred, wherein R³ is an amino group.

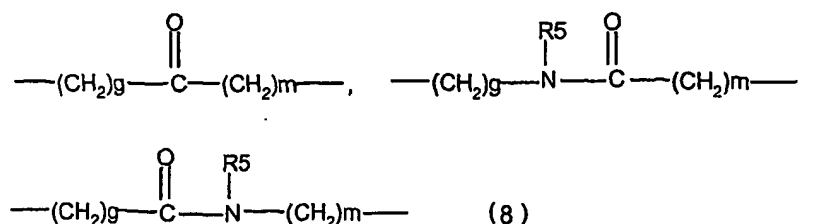
Also of special interest are those combinations wherein b) comprises at least one compound from the group of compounds of formula II), wherein Q is selected from the structures illustrated in formula (5); A is an optionally

substituted hetero ring, especially optionally substituted pyridyl group; most preferred, wherein X is selected from the structures illustrated in formula (7):



wherein e, g and R⁴ are as defined above; most preferred wherein n is 1 and R¹ and R² are a hydrogen atom; most preferred, wherein R³ is an amino group.

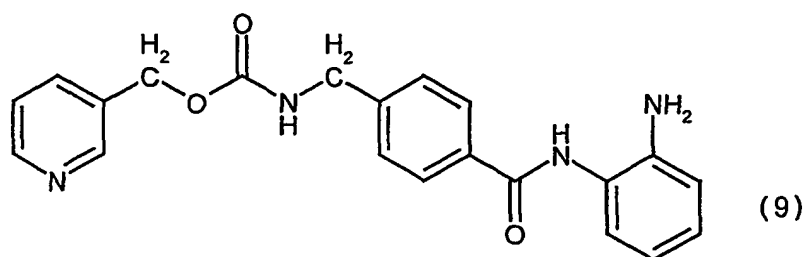
Interesting combinations wherein b) comprises at least one compound from the group of compounds of formula II), wherein Q is selected from the structures illustrated in formula (5); A is an optionally substituted hetero ring, especially optionally substituted pyridyl group; most preferred, wherein X is selected from the structures illustrated in formula (8):

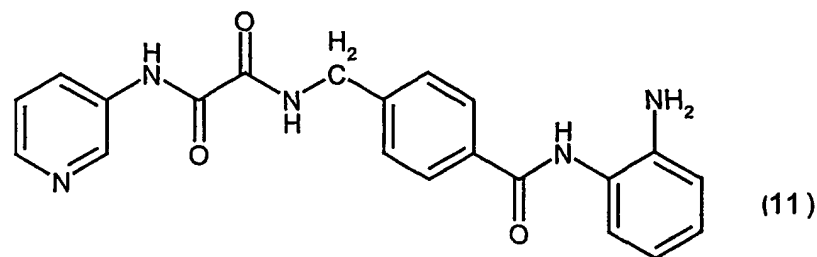
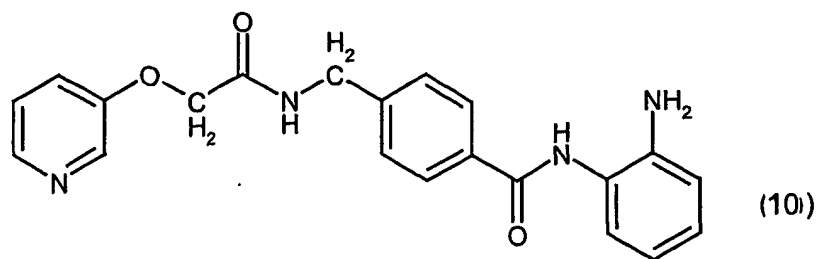


wherein g, m and R⁵ are as defined above; most preferred wherein n is 1 and R¹ and R² are a hydrogen atom; most preferred, wherein R³ is an amino group.

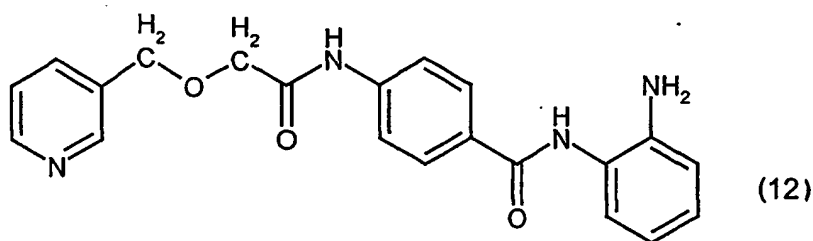
Of special interest are also those combinations, wherein b) comprises at least one compound from the group of compounds of formula II), wherein n is zero, and most preferred, Q is selected from the structures illustrated in formula (5); and most preferred, wherein A is an optionally substituted hetero ring; most preferred, wherein A is an optionally substituted pyridyl group; most preferred, wherein R¹ and R² are a hydrogen atom; most preferred, wherein R³ is an amino group.

Selected compounds of general formula II are for example the following compounds:

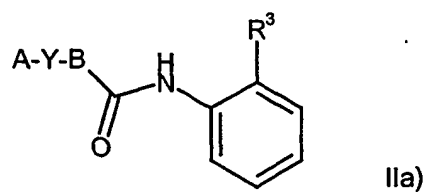




and



20 The inventive combination may also comprise as part b) a compound of general Formula IIa)



25 wherein A and R³ are as defined above; B is an optionally substituted a phenyl or heterocycle group; Y is a moiety having --CO--, --CS--, --SO-- or --SO₂-- which is linear, cyclic or their combination and links A and B; and in which the distances between the centroid of ring B (W1), the centroid of ring A (W2) and

an oxygen or sulfur atom as a hydrogen bond acceptor in the moiety Y (W3) can be as follows; W1-W2=6.0 to 11.0 Å, W1-W3=3.0 to 8.0 Å, and W2-W3=3.0 to 8.0 Å; preferably W1-W2=7.0 to 9.5 Å; W1-W3 is 3.0 to 5.0 Å; and W2-W3 is 5.0-8.0 Å; or a pharmaceutically acceptable salt thereof.

5

Interesting combinations are those combinations wherein b) comprises at least one compound from the group of compounds of formula IIa), wherein A is an optionally substituted heterocycle; R³ is an amino group; and Y is a moiety having --CO-- which is linear, cyclic or their combination and links A and B.

10

Further, interesting combinations are those combinations wherein b) comprises at least one compound from the group of compounds of formula IIa), wherein B is an optionally substituted phenyl; W1-W2 is 7.0 to 9.5 Å; W1-W3 is 3.0 to 5.0 Å; and W2-W3 is 5.0 to 8.0 Å.

15

The invention also comprises the combination with anti-hormones, such as anti-oestrogens and anti-progesterones, as described in EP 0062 503, and anti-androgenes, as described in US 5,053,405 and DE 31 211 52.

20

The inventive combination comprising at least one compound of formula I-A or I-AA, and at least one compound of formula II) or IIa), and at least one anti-hormonal compound can be used as a combined preparation simultaneously, separately or sequentially.

25

The invention further comprises the use of a combination for the manufacture of a medicament for a therapeutic application for treating cancer and tumors, wherein the compound(s) of formula I-A or I-AA, and compound(s) of general formula II) or IIa), and the anti-hormonal compound(s) are simultaneously, separately or sequentially used.

30

The invention further comprises a combination comprising

- a) 9cis-retine acid (CRA), 13cis-retine acid, or a derivative thereof
and
- b) at least one compound of general formula II)
and
- 5 c) at least one anti-hormonal compound taken from the groups comprising
anti-oestrogen, anti-progesterone and anti-androgen compounds,
overcome the disadvantages of the known single compounds.
- 10 Of special interest are those combinations comprising
- a) 9cis-retine acid (CRA)
and
- b) at least one compound of general formula II)
and
- 15 c) at least one anti-hormonal compound taken from the groups comprising
anti-oestrogen, anti-progesterone and anti-androgen compounds,
overcome the disadvantages of the known single compounds.

20

Of most interest are those combinations comprising

- a) 9cis-retine acid (CRA),
and
- b) 3-pyridylmethyl-N-{4-[(2-amino-phenyl)carbamoyl]benzyl}-carbamate,
25 and
- c) tamoxifen.

9cis-retine acid (CRA), 13cis-retine acid, or a derivative thereof are known in
the treatment of different skin diseases

30

The inventive combinations can be used with at least one pharmaceutically
acceptable diluent or carrier.

The invention also comprises a kit, comprising the inventive pharmaceutically active combination wherein the compound(s) of general formula I-A or I-AA, and compound(s) of general formula II) or IIa), and the anti-hormonal compound(s)
5 as a combined preparation are simultaneously, separately or sequentially used.

The inventive combinations can be used for enteral administration, such as nasal, buccal, rectal or, especially, oral administration, and for parenteral administration, such as intravenous, intramuscular or subcutaneous
10 administration, to warm-blooded animals, especially, humans, are especially preferred. The compositions comprise the active ingredient alone or, preferably, together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends upon the disease to be treated and upon the species, gender, age, weight, and individual condition, the individual pharma-cokinetic
15 data, and the mode of administration.

The inventive combinations can also used as a method for the prophylactic or especially therapeutic management of the human or animal body, to a process for the preparation thereof (especially in the form of compositions for the
20 treatment of tumours) and to a method of treating tumour diseases, especially those mentioned hereinabove.

In the preferred embodiment, the pharmaceutical combinations is suitable for administration to a warm-blooded animal, especially humans or commercially
25 useful mammals suffering form a disease responsive to an inhibition of angiogenesis or of VEGF-receptor tyrosine kinase, for example psoriasis or especially a neoplastic disease, and comprises an effective quantity of a compounds for the inhibition of angiogenesis or of VEGF-receptor tyrosine kinase, or a pharmaceutically acceptable salt thereof, if salt-forming groups are
30 present, together with at least one pharmaceutically acceptable carrier.

The inventive combinations can be used for the prophylactic or especially

therapeutic management of neoplastic and other proliferative diseases of a warm-blooded animal, especially a human or a commercially useful mammal requiring such treatment, especially suffering from such a disease.

- 5 The inventive combinations comprise from approximately 1% to approximately 95% active ingredient, single-dose administration forms comprising in the preferred embodiment from approximately 5% to approximately 20% active ingredient. Unit dose forms are, for example, coated and uncoated tablets, ampoules, vials, suppositories or capsules. Further dosage forms are, for
10 example, ointments, creams, pastes, foams, tinctures, lip-sticks, drops, sprays, dispersions, etc. Examples are capsules containing from about 0.05 g to about 1.0 g active ingredients.

The pharmaceutical combination of the present invention are prepared in a
15 manner known *per se*, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes.

Preference is given to the use of solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions
20 or suspensions which, for example in the case of lyophilized compositions comprising the active ingredients alone or together with a carrier, for example mannitol, can be made up before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating
25 osmotic pressure and/or buffers and are prepared in a manner known *per se*, for example by means of conventional dissolving and lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, for example Tween 80
30 [polyoxyethylene(20)sorbitan mono-oleate; trademark of ICI Americas, Inc. USA].

Suspensions in oil comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. In respect of such, special mention may be made of liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tripdecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of anti-oxidants, for example vitamin E, β -carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of these fatty acid esters has a maximum of 6 carbon atoms and is a monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. As fatty acid esters, therefore, the following are mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, „Labrafil M 2375“ (polyoxyethylene glycerol trioleate from Gattefossé, Paris), „Labrafil M 1944 CS“ (unsaturated polyglycolized glycerides prepared by alcoholysis of apricot kernel oil and consisting of glycerides and polyethylene glycol ester; Gattefossé, France), „Labrasol“ (saturated polyglycolized glycerides prepared by alcoholysis of TCM and consisting of glycerides and polyethylene glycol ester; Gattefossé, France), and/or „Miglyol 812“ (triglyceride of saturated fatty acids of chain length C_8 to C_{12} from Hüls AG, Germany), but especially vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The manufacture of injectable preparations is usually carried out under sterile conditions, as is filling, for example into ampoules or vials, and the sealing of the containers.

Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, if desired granulating a resulting mixture, and processing the mixture of granules,

if desired or necessary, by the inclusion of additional excipients, to form tablets or tablet cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Tablet cores can be provided with suitable, optionally enteric, coatings through the use of, *inter alia*, concentrated sugar solutions, which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixture, or for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetyl cellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or

propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Other oral dosage forms are, for example syrups prepared in customary manner which comprise the active ingredient, for example, in suspended form and in a concentration of about 5% to 20%, preferably about 10%, or in similar concentration that provides a suitable single dose, for example, when administered in measures of 5 or 10 ml. Also suitable are, for example, powdered or liquid concentrates for the preparation of shakes, for example in milk. Such concentrates may also be packaged in single-dose units.

Pharmaceutical compositions suitable for rectal administration are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For preteral administration, aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers, are especially suitable. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents.

25

Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or micro-bicides, such as sorbic acid or benzoic acid.

30

The invention relates likewise to a process or a method for the treatment of one of the pathological conditions mentioned hereinabove, especially a disease which responds to an inhibition of the VEGF-receptor tyrosine kinase or an inhibition of angiogenesis, especially a corresponding neoplastic disease or also psoriasis. The combination can be administered as such or especially in the form of pharmaceutical compositions, prophylactically or therapeutically, preferably in an amount effective against the said diseases, to a warm-blooded animal, for example a human, requiring such treatment. In case of an individual having a bodyweight of about 70 kg the daily dose administered is from approximately 0.1 g to approximately 5 g, preferably from approximately 0.5 g to approximately 2 g, of a compound of the present invention.

The present invention relates especially also to the use of the combination, as such or in the form of a pharmaceutical formulation with at least one pharmaceutically acceptable carrier for the therapeutic and also prophylactic management of one or more of the diseases mentioned hereinabove, especially a neoplastic disease or also psoriasis, more especially if the disease responds to an inhibition of angiogenesis or an inhibition of VEGF-receptor tyrosine kinase.

The present invention relates especially also to the use of the combination, as such or in the form of a pharmaceutical formulation with at least one pharmaceutically acceptable carrier for the therapeutic and also prophylactic management of one or more of the diseases mentioned hereinabove, preferably a disease which responds to an inhibition of VEGF-receptor tyrosine kinase or an inhibition of angiogenesis, especially a neoplastic disease or also psoriasis, more especially if the said disease responds to an inhibition of VEGF-receptor tyrosine kinase or angiogenesis.

The present invention relates especially also to the use of the combination for the preparation of a pharmaceutical formulation for the therapeutic and also prophylactic management of one or more of the diseases mentioned

hereinabove, especially a neoplastic disease or also psoriasis, more especially if the disease responds to an inhibition of VEGF-receptor tyrosine kinase or angiogenesis.

5 The combination of this invention has differentiation-inducing effects and thus is useful as a therapeutic and/or improving combined agent to a variety of diseases such as malignant tumors, autoimmune diseases, dermatologic diseases and parasitism.

10 As used herein, a "malignant tumor" includes hematologic malignancy such as acute leukemia, malignant lymphoma, multiple myeloma and macroglobulinemia as well as solid tumors such as colon cancer, cerebral tumor, head and neck tumor, breast carcinoma, pulmonary cancer, esophageal cancer, gastric cancer, hepatic cancer, gallbladder cancer, bile duct cancer,
15 pancreatic cancer, neuroblastoma, renal cell carcinoma, adrenocortical cancer, urinary bladder carcinoma, prostatic cancer, testicular tumor, ovarian carcinoma, uterine cancer, chorionic carcinoma, thyroid cancer, malignant carcinoid tumor, skin cancer, malignant melanoma, osteogenic sarcoma, soft tissue sarcoma, neuroblastoma, Wilms tumor and retinoblastoma.

20 An autoimmune disease includes rheumatism, such as rheumatoid arthritis, diabetes, systemic lupus erythematosus, human autoimmune lymphocytotoxic lymphadenopathy, immunoblastic lymphadenopathy, Crohn's disease and ulcerative colitis.

25 A dermatologic disease includes psoriasis, acne, eczema and atopic dermatitis.

Parasitism includes diseases such as malaria caused through vermination.

30 Further, the inventive combination can be used for the treatment of hemangioma, angiofibroma, diseases of the eyes, such as diabetic retinopathy, neovascular glaucoma, diseases of the kidney, such as

glomerulonephritis, diabetic nephropatic diseases, malignant nephrosclerosis, thrombotic microangiopathic syndrome, disposes of transplants and glomerulopathy, fibrotic diseases, such as liver cirrhosis, mesangial cell proliferative diseases and arteriosclerosis, injury of the nervous tissues, for inhibition of reocclusion of vascular systems after balloon catheter treatment, for artificial limbs, or after insert of mechanically devices for keeping open of vasculature, such as stents.

For the treatment of injury of the nervous tissues a rapid production of scars at the place of injury can be prevented. Thus, production of scars will be prevented before the axones can re-establish. Therefore a re-construction of nerves is possible.

Further, by using the inventive combination the ascites production within patients can be suppressed. Also, oedema resulted by VEGF can be suppressed.

Indications for the combination of this invention are not limited to these specific examples.

The active ingredient of the combination useful as a drug may be used in the form of a general pharmaceutical composition. The pharmaceutical composition maybe prepared with generally used diluents or excipients such as filler, extender, binder, moisturizing agent, disintegrator, surfactant and lubricant. The pharmaceutical composition may have a variety of dosage forms depending on its therapeutic purpose; typically tablet, pill, powder, solution, suspension, emulsion, granule, capsule, injection (e.g., solution, suspension) and suppository.

For preparing tablets, a variety of carriers well-known in the art may be used. Such a carrier includes excipients such as lactose, glucose, starch, calcium carbonate, kaoline, crystalline cellulose and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose and polyvinyl pyrrolidone; disintegrators such as dried starch, sodium alginate, powdered

agar, calcium carmelose, starch and lactose; disintegration retarders such as sucrose, cocoa butter and hydrogenated oil; absorption promoters such as quaternary ammonium base and sodium lauryl sulfate; moisturizing agents such as glycerin and starch.; adsorbents such as starch, lactose, kaoline, bentonite, colloidal silicic acid; and glidants such as talc, stearates and polyethylene glycol. The tablet may be, if necessary, one coated with a common coating; for example, sugar-coated tablet, gelatin-coated tablet, enteric coated tablet, film-coated tablet, double-layer tablet and micro layer tablet.

10 In forming pills, a variety of carriers well-known in the art may be used. Such a carrier includes excipients such as crystalline cellulose, lactose, starch, hydrogenated vegetable oil, kaoline and talc; binders such as powdered acacia, powdered tragacanth gum and gelatin; disintegrators such as calcium carmelose and agar.

15

Capsule may be prepared by blending an active ingredient with a variety of the above carriers as usual and filling the resulting blend into, for example, a hard or soft gelatin capsule or the like.

20 For preparing injection, solution, emulsion and suspension are sterilized and preferably isotonic with blood. It may be prepared using diluents commonly used in the art; for example, water, ethanol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxyisostearyl alcohol and polyoxyethylene sorbitan fatty acid esters. The pharmaceutical preparation may contain sodium chloride necessary to prepare an isotonic solution, glucose or glycerin, as well as usual solubilizers, buffers and soothing agents.

25

Suppository may be formed using a variety of well-known carriers; for example, semi-synthetic glyceride, cocoa butter, higher alcohols, higher alcohol esters and polyethylene glycol.

30

Furthermore, the pharmaceutical combination may contain coloring agents,

preservatives, perfumes, flavors, sweeteners and/or other drugs.

The amount of the active ingredient in the pharmaceutical combination of this invention may be, as appropriate, selected from a wide range with no
5 limitations, and is generally about 1 to 70% by weight in the composition, preferably about 5 to 50% by weight.

An administration route of the pharmaceutical combination is not limited, and selected depending on patient's age, sex, severity of disease and other
10 conditions. For example, tablet, pill, solution, suspension, emulsion, granule and capsule may be orally administered; injection may be intravenously administered solely or in combination with a common infusion fluid such as glucose, amino acids and the like, or if necessary, intramicro scularly, subcutaneously or intraperitoneally as a sole preparation. Suppository may be
15 intrarectally administered.

Dose of the pharmaceutical combination of this invention may be selected, depending on their dosage form, patient's age, sex and severity of disease, and other conditions, as appropriate, but the amount of the active ingredient may be
20 generally about 0.0001 to 100 mg/kg a day. It is recommended that a unit dosage form may contain about 0.001 to 1000 mg of the active ingredient.

Biological Examples

Example 1

- 5 **Combination therapy with different biomodulators on a colorectal carcinoma model in Wag rats**

Combination of 1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine
hydrochloride (ZK) and 3-pyridylmethyl-N-{4-[(2-amino-phenyl)-
10 carbamoyl]benzyl}carbamate (MS) with Tamoxifen (TAM)

CC cells CC531 were cultured in vitro (10th -15th passage) and implanted into the liver of adult (250g) immunocompetent Wag rats (n/group = 12). Between the seventh and the 28th postoperative day the rats received either a placebo
15 therapy, the conventional chemotherapy 5-fluoruracil (5FU, 10mg/kg) or the following biomodulators alone or in combination: the VEGF receptor antagonist 1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride (ZK) (50mg/kg), the histone deacetylase inhibitor 3-pyridylmethyl-N-{4-[(2-amino-phenyl)carbamoyl]benzyl}carbamate (MS) dose and Tamoxifen (TAM) (TAM:
20 3mg/kg KG i.p.). Apoptosis rate was assessed using a the TUNEL method on paraformaldehyd fixed tumor material.

The results demonstrate that untreated rats developed a tumor reaching a diameter of 31 mm after 4 weeks. Metastazation into lung, kidneys, spleen and peritoneum occurred time dependently. After 5-6 weeks untreated rats died or
25 had to be killed due to ascites and reduced condition. The conventional chemotherapy 5FU did not reduce tumor growth. Similarly, the single agents ZK, MS, TAM showed no significant reduction of primary tumor volume. However, the dual therapy ZK/MS reduced tumor growth and metastasis significantly with no impairment of overall health conditions. The triple therapy
30 further reduced tumor volume, but induced a loss of weight of 10 ± 10% BW. Further side effects, such as unusual behaviour or reduced condition of ruffled fur did not appear. Effective treatment increased apoptotic TUNEL positive cells

compared to controls.

The results are shown in table I.

5

Table I

Compound	Tumor Volume *)
	[%]
5-Fluorouracil (5FU)	85 ± 19
Tamoxifen (TAM)	90 ± 10
(4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]-ammonium hydrogen succinate (ZK)	94 ± 20
3-pyridylmethyl-N-{4-[(2-amino-phenyl)-carbamoyl]benzyl}-carbamate (MS)	80 ± 23
ZK/MS	35 ± 11
ZK/MS/TAM	2 ± 0,5

10 *) % ± SD compared to untreated controls)

The results show a synergistic effect of the combination of ZK/MS and ZK/MS/Tamoxifen. There is clearly superiority over the single agents if applied
15 alone.

Example 2

Combination therapy with different biomodulators on endothelial cell proliferation

5

Combination of 1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride (ZK) and 3-pyridylmethyl-N-{4-[(2-amino-phenyl)-carbamoyl]benzyl}carbamate (MS)

10

Preparation of Microvascular Dermal Endothelial Cells

Microvascular Dermal Endothelial Cells were prepared and the proliferation was measured according to the method of Piossek C, Schneider-Mergener J,

15

Schirner M, Vakalopoulou E, Germeroth L, Thierauch KH.

Vascular endothelial growth factor (VEGF) receptor II-derived peptides inhibit VEGF (J Biol Chem. 1999 Feb 26;274(9):5612-9).

20

Preparation of Microvascular Endothelial Cells from Human Foreskin

Preparation of magnetic beads according to Jackson *et al.* (Ref. 44, 10 million Dynabeads (anti-mouse Ig coated by means of an DNA linker)) were washed with PBS/bovine serum albumin (BSA) three times using the magnetic device.

25

Anti-CD31 antibody (Immunotech, Westbrook, ME) was added at a concentration of 3.5 µg/10 million beads and shaken for 30 min. The suspension was washed five times with PBS/BSA and stored in 1.25 ml of 0.01% azide containing PBS/BSA at 4° C. Beads were washed directly before use to remove azide.

30

Proliferation of Microvascular Endothelial Cells

50 000 cells were plated into a 24-well plate in full medium based on M199. After 2 h the medium was changed to 3% human serum. The next morning various amounts of VEGF₁₆₅ and inhibitors were added. After 3 days in culture the cells were washed and 1% rose bengal in 30% ethanol was added. After 5 min the dye solution was removed, and the cells were washed three times thoroughly with PBS and lysed with 0.1% sodium dodecyl sulfate in PBS. Optical density of the resulting solutions was determined at 560 nm.

10

For the present experiment, the cells that have been held in low serum medium over night and were then treated with various combinations of MS-275 (MS) and PTK, ranging from 3×10^{-8} M to 3×10^{-6} M. As can be seen in figure 1 (Fig. 1), the inhibitory curve of ZK was shifted synergistically to the left in the presence of small concentrations of MS (MS-275).

15

As proliferation of endothelial cells is a most prominent event in angiogenesis, its inhibition is resulting in improved inhibition of cancer growth. The application of both agents will allow for a dose reduction of both agents in the patient. This is beneficial for the patient as either toxicity can be reduced by reduced dose or efficacy can be increased by dosing both drugs simultaneously.

20

Example 3**Combination of 9cis-retine acid (CRA) and 3-pyridylmethyl-N-{4-[(2-amino-phenyl)-carbamoyl]benzyl}carbamate (MS) with Tamoxifen (TAM)**

5

CC531 and HCT116 cells were cultured as described in Example 1. The experiment was carried out under the same conditions as described in Example 1.

10 The % of apoptosis induction after 72 h was determined. The data were calculated on basis of three separate experiments.

The results are shown in the following table:

Compound	CC531	HCT116
TAM/CRA 10-5M	7 ± 3	14 ± 3
TAM/CRA/MS 10-5M	34 ± 9	75 ± 12

15

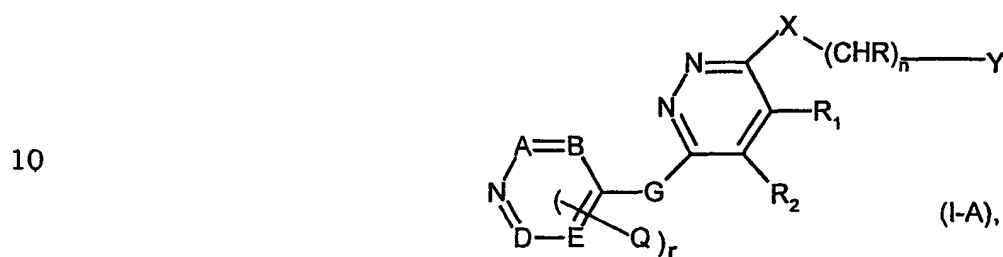
The results show a significant apoptose induction of the combination of CRA/MS/Tamoxifen in both cell lines.

20

What is claimed is:

1. A combination comprising

5 a) at least one compound from the group of compounds of formula I-A



wherein

15 r is 0 to 2,

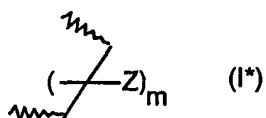
n is 0 to 2,

m is 0 to 4,

R₁ and R₂ (i) are lower alkyl or

(ii) together form a bridge in subformula I*

20

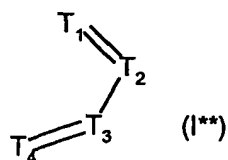


the binding being achieved via the two terminal carbon atoms,

25 or

(iii) together form a bridge in subformula I**

30



wherein one or two of the ring members T₁, T₂, T₃ and T₄ can

be nitrogen, and the others are in each case CH, and the binding is achieved via T₁ and T₄

A, B, D and E are, independently of one another, N or CH, with the stipulation that not more than 2 of these radicals are N;

G is lower alkylene, lower alkylene substituted by acyloxy or hydroxy, -CH₂-O-, CH₂-S-, -CH₂-NH-, oxa (-O-), thia (-S-), or imino (-NH-);

Q is lower alkyl;

R is H or lower alkyl;

X is imino, oxa, or thia;

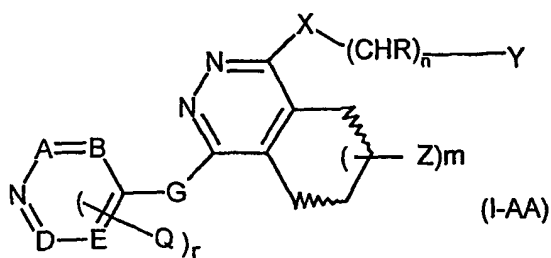
Y is unsubstituted or substituted aryl, pyridyl, or cycloalkyl; and

Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono-or N, N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or alkylphenylsulfinyl, substituents Z being the same or different from one another if more than 1 radical Z is present;

and wherein the bonds characterized, if present, by a wavy line are either single or double bonds;

or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom;

with the stipulation that, if Y is pyridyl or unsubstituted
 cycloalkyl, X is imino, and the remaining radicals are as
 defined, G is selected from the group comprising lower
 alkylene, -CH₂-O-, -CH₂-S-, oxa and thia; or a salt thereof;
 or
 at least one compound from the group of compounds of formula
 I-AA



wherein

r is 0 to 2,

n is 0 to 2,

m is 0 to 4,

A, B, D and E are, independently of one another, N or CH,
 with the stipulation that not more than 2 of these radicals are N;

G is lower alkylene, -CH₂-O-, -CH₂-S-, CH₂-NH-, oxa, thia, or
 imino;

Q is methyl;

R is H or lower alkyl;

X is imino, oxa, or thia;

Y is unsubstituted or substituted aryl, pyridyl, or cycloalkyl; and

5 Z is amino, mono- or disubstituted amino, halogen, alkyl, substituted alkyl, hydroxy, etherified or esterified hydroxy, nitro, cyano, carboxy, esterified carboxy, alkanoyl, carbamoyl, N-mono-or N,N-disubstituted carbamoyl, amidino, guanidino, mercapto, sulfo, phenylthio, phenyl-lower alkylthio, alkylphenylthio, phenylsulfonyl, phenyl-lower alkylsulfinyl or
10 alkylphenylsulfinyl, substituents Z being the same or different from one another if more than 1 radical Z is present;

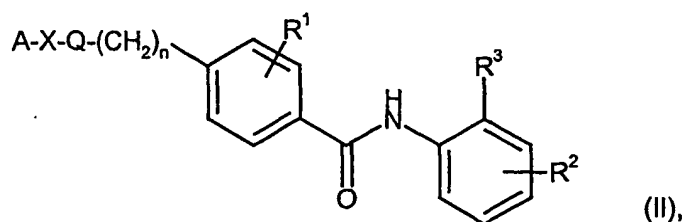
and wherein the bonds characterized by a wavy line are either single or double bonds;

15 or an N-oxide of the defined compound, wherein 1 or more N atoms carry an oxygen atom;

with the stipulation that, if Y is pyridyl or unsubstituted
20 cycloalkyl, X is imino, and the remaining radicals are as defined, G is selected from the group comprising lower alkylene, -CH₂-O-, -CH₂-S-, oxa and thia; or a salt thereof;

and

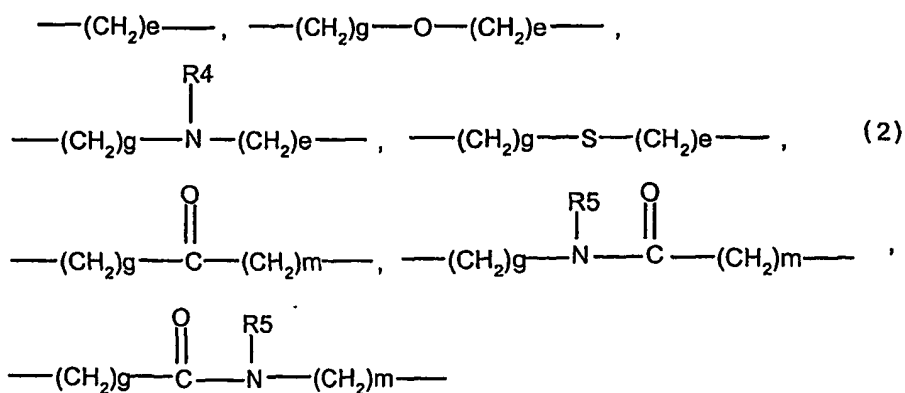
25 b) at least one compound from the group of compounds of formula II)



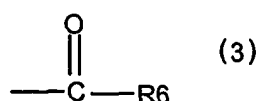
wherein

A is an optionally substituted phenyl group or an optionally substituted heterocyclic group wherein the substituent(s) for the phenyl group or the heterocyclic group is (are) 1 to 4 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;

X is a bond or a moiety having the following structure



wherein e is an integer of 1 to 4; g and m are independently an integer of 0 to 4; R⁴ is a hydrogen atom or an optionally substituted alkyl group having 1 to 4 carbons, or the acyl group represented by formula (3)



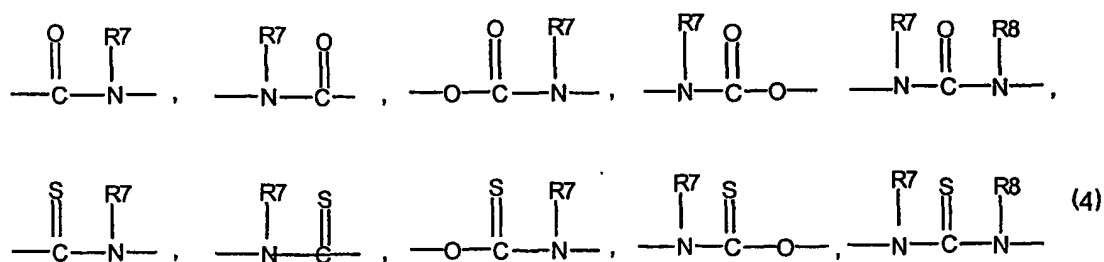
wherein R⁶

is an optionally substituted alkyl group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a phenyl group or a heterocyclic group; R⁵ is a hydrogen atom or an optionally substituted alkyl group having 1 to 4 carbons;

n is an integer of 0 to 4, provided that when X is a bond, n is not zero;

wherein Q

is a moiety having a structure selected from those illustrated in formula (4)



wherein R⁷ and R⁸ are independently hydrogen atom or an optionally substituted alkyl group having 1 to 4 carbons;

R¹ and R² are independently a hydrogen atom, a halogen atom, a hydroxyl group, an amino group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino

group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group or an alkoxy carbonyl group having 1 to 4 carbons;

5

R^3 is a hydroxyl or amino group or a pharmaceutically acceptable salt thereof.

- 10 2. A combination comprising
- a) at least one compound of general formula I-A) or formula I-AA), according to claim 1
- and
- b) at least one compound of general formula II), according to claim
- 15 1
- and
- c) at least one anti-hormonal compound taken from the groups comprising anti-oestrogen, anti-progesterone and anti-androgen compounds.

20

3. A combination according to claim 2, wherein the anti-hormonal compounds are
- i) at least one anti-hormonal compound taken from the group of
- 25 anti-oestrogen compounds:
- (Z)-2-[p-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethylamine (tamoxifen),
- 1-[2-[4-(6-methoxy-2-phenyl-3,4-dihydro-1-naphthyl)phenoxy]-ethyl]-pyrrolidine hydrochloride (nafoxidine),
- 30 1-[p-(2-diethylaminoethoxy)phenyl]2-(p-methoxyphenyl)-1-phenylethanol (Mer 25),
- 11 α -methoxy-17 α -ethynyl-1,3,5(10)-estratriene-3,17 β -diol,

16 β -ethylestradiol,

11-(3,17 β -dihydroxy-1,3,5(10)-estratrien-7 α -yl)undecanoic-
acid(N-butyl-N-methyl)amide,

[6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl-[2-
(piperidinyl)ethoxy]phenyl]methanone,

5 ii) at least one anti-hormonal compound taken from the group of
anti progesterone compounds

11 β -[(4-N,N-dimethylamino)phenyl]-17 β -hydroxy-17 α -propynyl-
4,9(10) estradien-3-one,

10 11 β -[(4-N,N-dimethylamino)phenyl]-17 β -hydroxy-18-methyl-
17 α -propynyl-4,9(10)-estradien-3-one,

11 β -[(4-N,N-dimethylamino)phenyl]-17 α β -hydroxy-17 α -
propynyl-D-homo-4,9(10)-16-estratrien-3-one,

15 11 β -p-methoxyphenyl-17 β -hydroxy-17 α -ethynyl-4,9(10)-
estradien-3-one,

11 β -(4-dimethylaminophenyl)-17 α -hydroxy-17 β -(3-
hydroxypropyl)-13-methyl-4,9-gonadien-3-one,

11 β -(4-dimethylaminophenyl)-17 α -hydroxy-17-(3-
hydroxypropyl)-13 α -estra-4,9-dien-3-one (onapristone),

20 and

iii) at least one anti-hormonal compound taken from the group of
anti-androgen compounds:

25 6-chloro-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-
dione,

6-chloro-17-hydroxypregna-4,6-diene-3,20-dione,

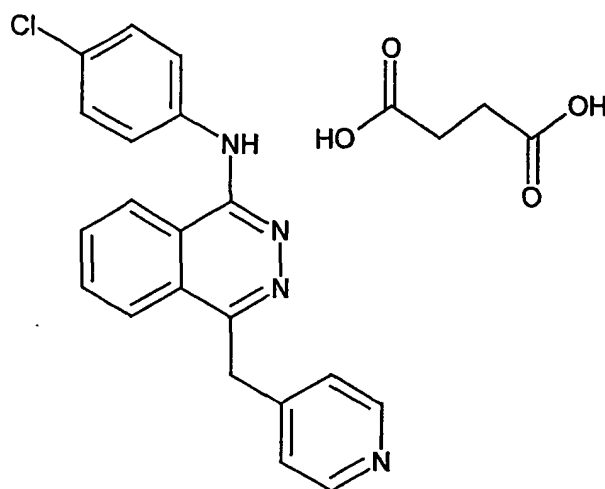
6-chloro-17-hydroxypregna-1,4,6-triene-3,20-dione,

6-chloro-3,17-dihydroxy-1 α ,2 α -methylenepregna-4,6-diene-20-
30 one,

- 6-chloro-3-methoxy-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-20-one,
 6-fluoro-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-dione,
 5 17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-dione,
 4,6-dichloro-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-dione,
 6-chloro-17-hydroxy-1 α ,2 α -methylenepregna-4,6-diene-3,20-dione acetate (cyproterone acetat),
 10 6-chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate (chlormadione acetate),
 6-chloro-17 $\alpha\beta$ -acetoxo-17 $\alpha\alpha$ -methyl-1 α ,2 α -methylene-D-homo-4,6-androstadiene-3,17-dione,
 6-chloro-17 α -acetoxo-17 β -methyl-1 α ,2 α -methylene-D-homo-4,6-androstadiene-3,17a-dione,
 15 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-propionamide (flutamide),
 2-hydroxy-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-propionamide,
 20 2-methyl-4-[4-nitro-3-(trifluoromethyl)phenyl]-5,6-dihydro-2H-1,2,4-oxadiazin-3-one,
 6 β ,7 β ,15 β ,16 β -dimethylen-3-oxo-17 α -pregn-4-ene-21,17-carbolactone (dihydrospirorenone).
- 25 4. A combination according to claims 2 and 3, wherein the antihormone compounds are tamoxifen, onapristone, and dihydrospirorenone, or derivatives thereof.
5. A combination according to any of claims 2 to 4, comprising
 30 a) 1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine hydrochloride or (4-Chlorophenyl)[4-(4-pyridylmethyl)-phthalazin-1-yl]-

ammonium hydrogen succinate (ZK)

b)



and

b) 3-pyridylmethyl-N-{4-[(2-amino-phenyl)carbamoyl]benzyl}-
carbamate,

and

c) tamoxifen.

6. A combination according to any of claims 1 to 3 wherein a) comprises at
least one compound from the group of compounds of formula I-A,

wherein

r is 0 to 2,

n is 0 or 1,

m is 0 or 1,

A, B, D and E are in each case CH,

G is lower alkylene, especially methylene,

Q is methyl, which is bound to A, to D, or to A and D;

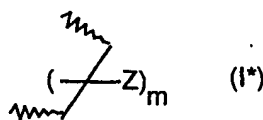
R is H or lower alkyl,

X is imino,

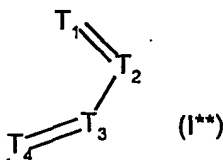
Y is phenyl, which is unsubstituted or substituted by one or two
substituents independently of one another from the group comprising
amino; lower alkanoylamino; halogen; lower alkyl; halogen-lower alkyl;

hydroxy; lower alkoxy; phenyl-lower alkoxy; cyano, or is pyridol;
 Z is amino; N-lower alkylamino; hydroxy-lower alkylamino; phenyl-lower
 alkylamino; N, N-di-lower alkylamino; n-phenyl-lower alkyl-N-lower
 alkylamino; N,N-di-lower alkylphenylamino; lower alkanoylamino; or a
 5 substituent from the group comprising benzoylamino or phenyl-lower
 alkoxycarbonylamino, wherein the phenyl radical in each case is
 unsubstituted or especially substituted by nitro or amino, or by halogen,
 amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano,
 carboxy, lower alkoxycarbonyl, lower alkanoyl or carbamoyl; or is
 10 halogen; and,
 the bonds characterized by a wavy line are in each case a double bond
 or in each case a single bond; or a salt thereof.

7. A combination according to any of claims 1 to 3 and 6, wherein a)
 15 comprises at least one compound from the group of compounds of
 formula I-A, wherein a), wherein
 r is 0 to 2,
 n is 0 or 1,
 m is 0 or 1,
 20 R₁ and R₂ (i) are lower alkyl or
 (ii) together form a bridge in subformula I*



the binding being achieved via the two terminal carbon atoms, or
 (iii) together form a bridge in subformula I**



wherein one of the ring members T₁, T₂, T₃ and T₄ can be nitrogen, and

the others are in each case CH, and the binding is achieved via T₁ and T₄

A, B, D and E are in each case CH, A, D and E are in each case CH and B is N;

G is lower alkylene, -CH₂-NH-, -CH₂-O-, hydroxymethylene, or benzolyoxymethylene,

Q is methyl, which is bound to A, to D, or to A and D;

R is H or lower alkyl,

X is imino, oxa, or thia,

Y is phenyl, which is unsubstituted or is substituted by one or two substituents independently of one another from the group comprising amino; lower alkanoylamino; halogen, lower alkyl; halogen-lower alkyl; hydroxy; lower alkoxy; phenyl-lower alkoxy; cyano; benzyloxy; lower alkenyl, C₈-C₁₂ alkoxy, lower alkoxy carbonyl, carbamoyl lower alkylcarbamoyl, lower alkanoyl, phenyloxy, halogen-lower alkyloxy, lower alkoxy carbonyl, lower alkylmercapto, halogen-lower alkylmercapto, hydroxy-lower alkyl, lower alkylsulfonyl, halogen-lower alkylsulfonyl, phenylsulfonyl, dihydroxybora, 2-methylpyrimidin-4-yl, oxazol-5-yl, 2-methyl-1,3-dioxolan-2-yl, 1H-pyrazol-3-yl, 1-methylpyrazol-3-yl, and lower alkylenedioxy bound to two adjacent C atoms, or is also pyridyl;

Z is amino; N-lower alkylamino; hydroxy-lower alkylamino; phenyl-lower alkylamino; N, N-di-lower alkylamino; n-phenyl-lower alkyl-N-lower alkylamino, N,N-di-lower alkylphenylamino; lower alkanoylamino; or a substituent from the group comprising benzoylamino or phenyl-lower

alkoxycaarbonylamino, wherein the phenyl radical in each case is unsubstituted or substituted by nitro or amino, or by halogen, amino, N-lower alkylamino, N,N-di-lower alkylamino, hydroxy, cyano, carboxy, lower alkoxy carbonyl, lower alkanoyl or carbamoyl; or is halogen; and, if present (in formula I-AA), the bonds characterized by a wavy line are in each case a double bond or in each case a single bond; or a salt thereof.

- 10 8. A combination according to any of claims 1 to 3 and 6 to 7, wherein a) comprises at least one compound from the group of compounds of formula I-A, wherein
- 15 r is 0,
n is 0 or 1,
m is 0;
A, B, D and E are in each case CH,
G is lower alkylene,
R is H;
X is imino,
- 20 Y is phenyl, which is unsubstituted or substituted by one or two substituents independently of one another from the group comprising amino; lower alkanoylamino; halogen; lower alkyl; halogen-lower alkyl; hydroxy; lower alkoxy; phenyl-lower alkoxy; and cyano; and the bonds characterized by a wavy line are double bonds; or a salt
- 25 thereof.

9. A combination according to any of claims 1 to 3 and 6 to 8 wherein a) comprises at least one compound from the group of compounds of formula I-A, wherein
- 30 r is 0,
n is 0 or 1,
m is 0;

A, B D and E are in each case CH,

G is methylene,

R is H,

X is imino,

5 Y is phenyl, 2-, 3- or 4-aminophenyl, 2-, 3- or 4-acetylamino-phenyl, 2-,
3- or 4-fluorophenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl,
2,3-, 2,4-, 2,5- or 3,4-dichlorophenyl, chlorofluorophenyl, 2-, 3- or 4-
methylphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-
hydroxyphenyl, 2-, 3- or 4- methoxycarbonyl, methoxychlorophenyl, 2-,
10 3- or 4- benzyloxyphenyl, or 2-, 3- or 4-cyanophenyl; and
the bonds characterized by the wavy line are double bonds; or a salt
thereof.

10. A combination according to any of claims 1 to 3 and 6 to 9, wherein a)
15 comprises at least one compound of the following selected compounds:

1-(4-Chloroanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4- Methylanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Chloroanilino)-4-(4-pyridylmethyl)phthalazine;
20 1-Anilino-4-(4-pyridylmethyl)phthalazine;
1-Benzylamino-4-(4-pyridylmethyl)phthalazine;
1-(4-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Benzoyloxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
25 1-(2-Methoxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Trifluoromethylanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Fluoroanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3-Hydroxyanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Hydroxyanilino)-4-(4-pyridylmethyl)phthalazine;
30 1-(3-Aminoanilino)-4-(4-pyridylmethyl)phthalazine;
1-(3,4-Dichloroanilino)-4-(4-pyridylmethyl)phthalazine;
1-(4-Bromoanilino)-4-(4-pyridylmethyl)phthalazine;

1-(3-Chloro-4-methoxyanilino)-4-(4-pyridylmethyl)phthalazine;

1-(4-Cyanoanilino)-4-(4-pyridylmethyl)phthalazine;

1-(3-Chloro-4-fluoroanilino)-4-(4-pyridylmethyl)phthalazine;

1-(3-Methylanilino)-4-(4-pyridylmethyl)phthalazine;

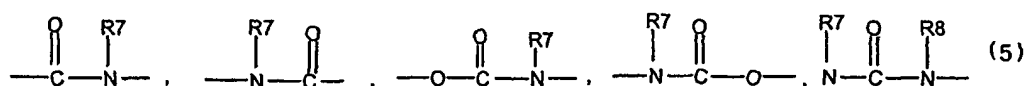
5 or in each case a pharmaceutically acceptable salt thereof.

11. A combination according to any of claims 1 to 4 and 6 to 10, wherein b) comprises at least one compound from the group of compounds of formula II), wherein n is an integer of 1 to 4.

10

12. A combination according to claim 11, wherein b) comprises at least one compound from the group of compounds of formula II), wherein Q is selected from the structures illustrated in formula (5):

15



wherein R^7 and R^8 are as defined above.

20

13. A combination according to claim 12, wherein b) comprises at least one compound from the group of compounds of formula II), wherein A is an optionally substituted hetero ring.

25

14. A combination according to claim 13 wherein b) comprises at least one compound from the group of compounds of formula II), wherein A is an optionally substituted pyridyl group.

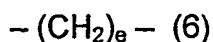
30

15. A combination according to claim 14 wherein b) comprises at least one compound from the group of compounds of formula II), wherein X is a direct bond.

16. A combination according to claim 15, wherein b) comprises at least one compound from the group of compounds of formula II), wherein R^1 and R^2 are a hydrogen atom.

5 17. A combination according to claim 16, wherein b) comprises at least one compound from the group of compounds of formula II), wherein R^3 is an amino group.

10 18. A combination according to claim 14, wherein b) comprises at least one compound from the group of compounds of formula II), wherein X is the structure represented by formula (6):



15

wherein e is as defined above.

19. A combination according to claim 18, wherein b) comprises at least one compound from the group of compounds of formula II), in which n is 1; and R^1 and R^2 are a hydrogen atom.

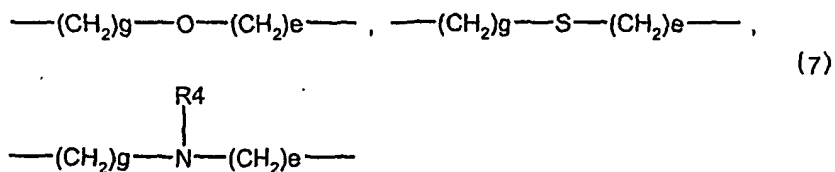
20

20. A combination according to claim 19, wherein b) comprises at least one compound from the group of compounds of formula II), wherein additionally R^3 is an amino group.

25

21. A combination according to claim 14, wherein b) comprises at least one compound from the group of compounds of formula II), wherein X is selected from the structures illustrated in formula (7):

30

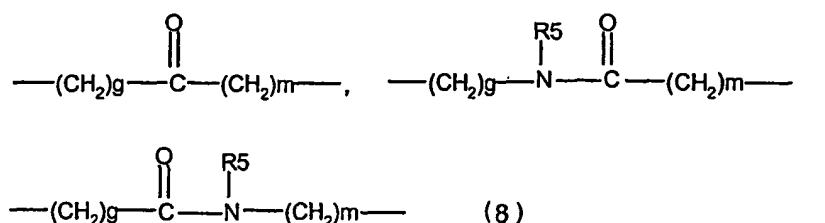


wherein e, g and R⁴ are as defined above.

22. A combination according to claim 21, wherein b) comprises at least one compound from the group of compounds of formula II), wherein n is 1 and R¹ and R² are a hydrogen atom.

23. A combination according to claim 22, wherein b) comprises at least one compound from the group of compounds of formula II), wherein R³ is an amino group.

24. A combination according to claims 14, wherein b) comprises at least one compound from the group of compounds of formula II), wherein X is selected from the structures illustrated in formula (8):



wherein g, m and R⁵ are as defined above.

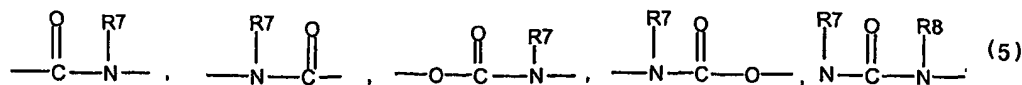
25. A combination according to claim 24, wherein b) comprises at least one compound from the group of compounds of formula II), wherein n is 1; and R¹ and R² are a hydrogen atom.

26. A combination according to claim 25, wherein b) comprises at least one compound from the group of compounds of formula II), wherein R³ is an amino group.

27. A combination according to any of claims 1 to 3 and 6 to 10, wherein b) comprises at least one compound from the group of compounds of

formula II), wherein n is zero.

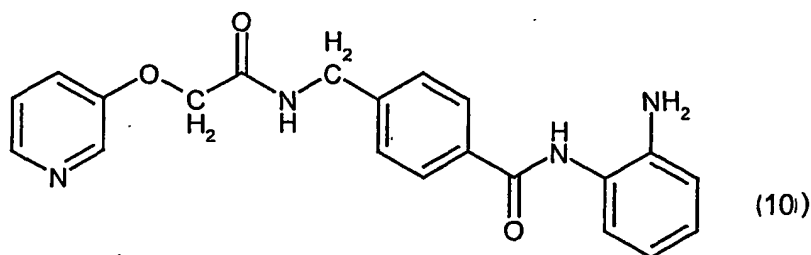
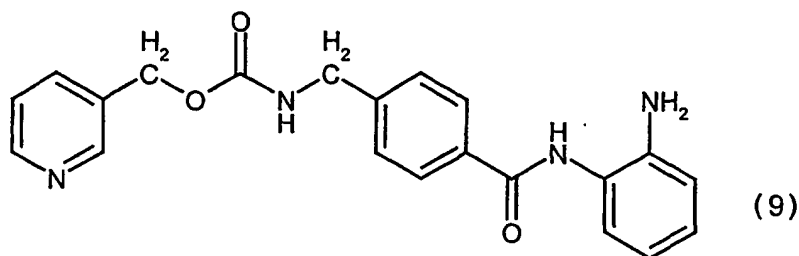
28. A combination according to claim 27, wherein b) comprises at least one compound from the group of compounds of formula II), wherein Q is selected from the structures illustrated in formula (5):

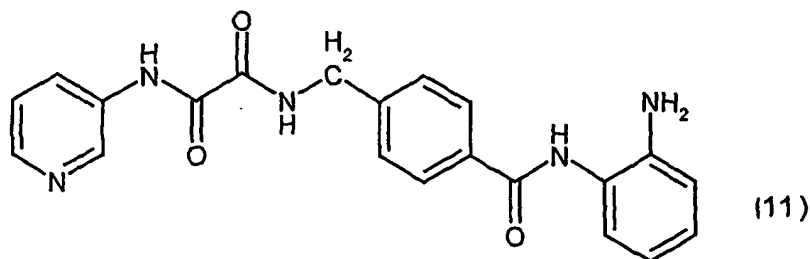


wherein R⁷ and R⁸ are as defined above.

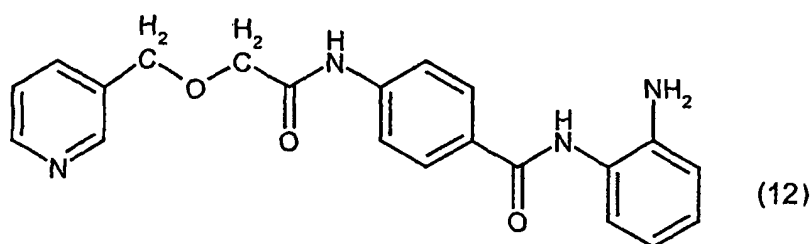
29. A combination according to any of claim 28, wherein b) comprises at least one compound from the group of compounds of formula II), wherein A is an optionally substituted pyridyl group, and wherein R¹ and R² are a hydrogen atom, and wherein R³ is an amino group.

30. A combination according to any of claims 1 to 4 and 6 to 29, wherein b) comprises at least one compound of the following structure:





and

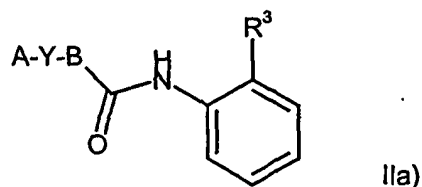


15 31. A combination comprising

a) at least one compound of formula I-A) or formula I-AA) according to claim 1,

and

20 b) at least one compound of general formula IIa)



25 wherein A and R³ are as defined above; B is an optionally substituted phenyl or heterocycle group; Y is a moiety having --CO--, --CS--, --SO-- or --SO₂-- which is linear, cyclic or their combination and links A and B; and in which the distances between the centroid of ring B (W1), the centroid of ring A (W2) and an oxygen or sulfur atom as a hydrogen bond acceptor in the moiety Y (W3) can be as follows; W1-W2=6.0 to

11.0 Å., W1-W3=3.0 to 8.0 Å., and W2-W3=3.0 to 8.0 Å., or a pharmaceutically acceptable salt thereof.

- 5 32. A combination comprising
- a) at least one compound of formula I-A) or formula I-AA) according to claim 1
- and
- b) at least one compound of general Formula IIa) according to claim 31
- 10 and
- c) at least one anti-hormonal compound according to any of claims 2 to 4.
- 15 33. A combination according to claims 31 and 32, wherein b) comprises at least one compound from the group of compounds of formula IIa), wherein A is an optionally substituted heterocycle; R³ is an amino group; Y is a moiety having —CO— which is linear or cyclic or their combination and links A and B.
- 20
34. A combination according to claim 33, wherein b) comprises at least one compound from the group of compounds of formula IIa), wherein B is an optionally substituted phenyl; W1-W2 is 7.0 to 9.5 Å; W1-W3 is 3.0 to
- 25 5.0 Å; and W2-W3 is 5.0-8.0 Å.
35. A combination according to any of claims 1 to 34, wherein at least one compound of formula I-A or I-AA, and at least one compound of formula
- 30 II) or IIa), and at least one anti-hormonal compound can be used as a combined preparation simultaneously, separately or sequentially.

36. A combination comprising

a) 9cis-retine acid (CRA), 13cis-retine acid, or a derivative thereof
and

b) at least one compound of general formula II)
and

c) at least one anti-hormonal compound taken from the groups
comprising anti-oestrogen, anti-progesterone and anti-androgen
compounds, overcome the disadvantages of the known single
compounds.

37. A combination according to claim 36, comprising

a) 9cis-retine acid (CRA)
and

b) at least one compound of general formula II)
and

c) at least one anti-hormonal compound taken from the groups
comprising anti-oestrogen, anti-progesterone and anti-androgen
compounds, overcome the disadvantages of the known single
compounds.

38. A combination according to any one of claims 36 to 37, comprising

a) 9cis-retine acid (CRA),
and

b) 3-pyridylmethyl-N-{4-[(2-amino-phenyl)carbamoyl]benzyl}-
carbamate,
and

c) tamoxifen.

39. Use of a combination for the manufacture of a medicament for a therapeutic application for treating cancer and tumors, wherein the compound(s) of formula I-A or I-AA, and compound(s) of general formula II) or Iia), and the anti-hormonal compound(s) are simultaneously, separately or sequentially used.
40. Use according to claim 39, with at least one pharmaceutically acceptable diluent or carrier.
41. A kit, comprising the combination according to any of claims 1 to 38, wherein the compound(s) of general formula I-A or I-AA, and compound(s) of general formula II) or Iia), and the anti-hormonal compound(s) as a combined preparation are simultaneously, separately or sequentially used.
42. Use of the combination according to any of claims 1 to 38, for the treatment of haemeangioma, angiofibroma, diseases of the eyes, such as diabetic retinopathie, neovascular glaucoma, diseases of the kidney, such as glomerulonephritis, diabetic nephropatic diseases, malignant nephrosclerosis, thrombotic microangiopathic syndrome, disposes of transplants and glomerulopathy, fibrotic diseases, such as liver cirrhosis, mesangialic cell proliferative diseases and arteriosclerosis, injury of the nervous tissues, for inhibition of reocclusion of vascular systems after balloon catheter treatment, for artificial limbs, or after insert of mechanically devices for keeping open of vasculature, such as stents.
43. Use of the combination according to any of claims 1 to 38, for the treatment of injury of the nervous tissues.
44. Use of the combination according to any of claims 1 to 38, for the

suppression of oedema resulted by VEGF.

45. A combination according to any one of claims 1 to 38, for use in a method for the treatment of the human or animal body.

5

46. A combination according to any one of claims 1 to 38, together with at least one pharmaceutically acceptable carrier, or excipient.

10

47. Use of a combination according to any one of claims 1 to 38, for the preparation of a pharmaceutical product for the treatment of a disease which responds to an inhibition of angiogenesis.

15

48. Use of a combination according to any one of claims 1 to 38, for the preparation of a pharmaceutical product for the treatment of a disease which responds to an inhibition of VEGF-receptor tyrosine kinase.

20

49. Use of a combination according to any one of claims 1 to 38, for the treatment of a disease which responds to an inhibition of VEGF-receptor kinase.

25

50. Use of a combination according to any one of claims 1 to 38, which is suitable for administration to a warm-blooded animal, especially suffering from a disease which responds to an inhibition of angiogenesis or of VEGF-receptor tyrosine kinase, comprising an effective quantity of the combination, together with at least one pharmaceutically acceptable carrier.

30

51. A method for treatment of disease which responds to an inhibition of VEGF-receptor tyrosine kinase or an inhibition of angiogenesis, which comprises administering a combination according to any one of claims 1 to 38, in a compound quantity effective against the said diseases, to a warm-blooded animal requiring such treatment in a compound quantity

suitable for the treatment of the said disease.

MEC proliferation in the presence of VEGFR-KI and HDAC-Inhibitor

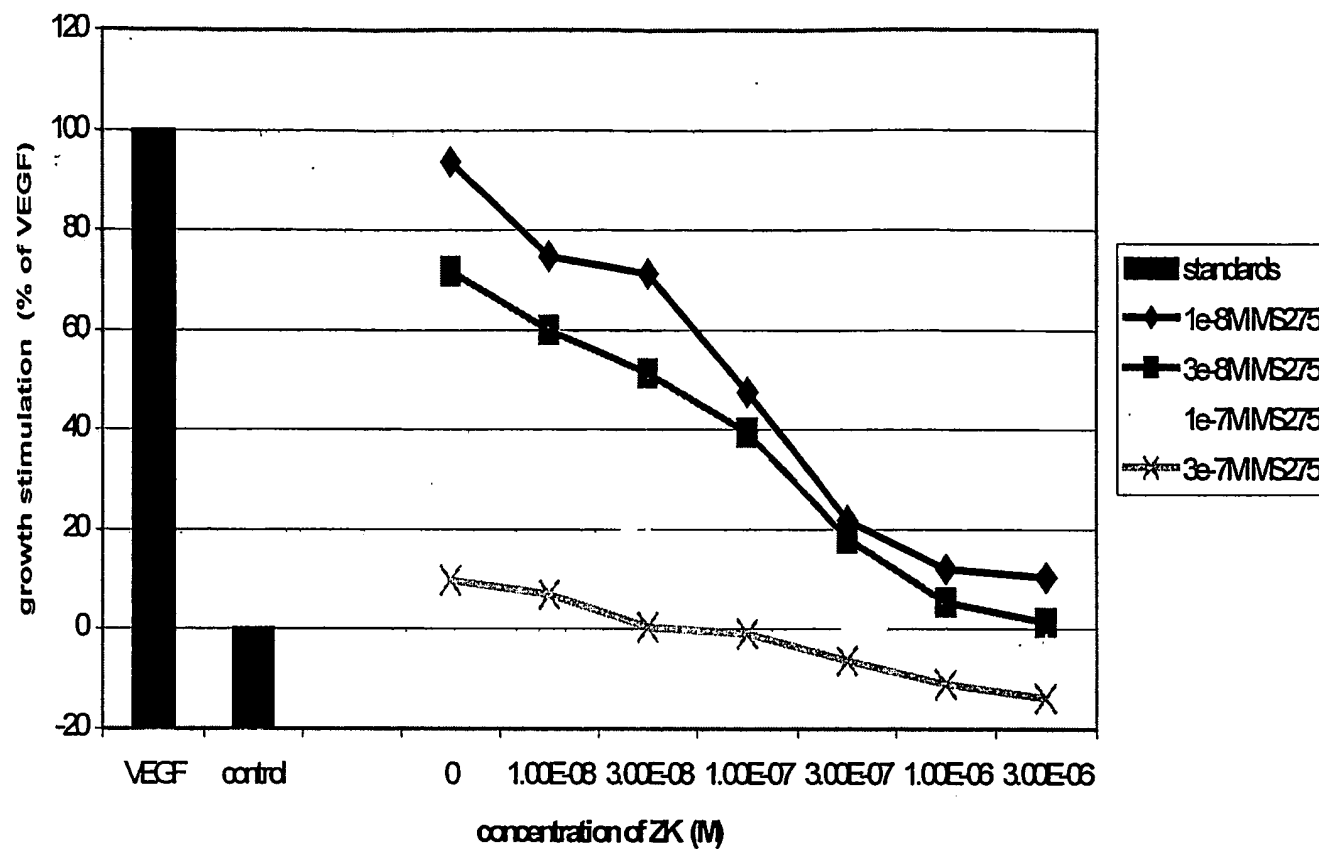


FIG. 1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/14071

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/502 A61K31/44 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 98/35958 A (NOVARTIS ERFIND VERWALT GMBH ; CIBA GEIGY AG (CH); TRAXLER PETER (CH);) 20 August 1998 (1998-08-20) cited in the application</p> <p>page 3, last paragraph - page 5, paragraph 5</p> <p>page 6, paragraph 2 - page 11, paragraph 6</p> <p>page 11, paragraph 7 - page 12, paragraph 3</p> <p>page 17, paragraph 2 - page 20, paragraph 2</p> <p>page 20, paragraph 5 - page 21, paragraph 1</p> <p>page 37, paragraph 4 - page 38, paragraph 2</p> <p>page 41, paragraph 6 - page 42, paragraph 4</p> <p style="text-align: center;">-----</p> <p style="text-align: center;">-/-</p>	1-30, 35, 39-51

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

27 April 2004

Date of mailing of the international search report

13/05/2004

Name and mailing address of the ISA

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Giacobbe, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/14071

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	ZGOURAS D ET AL: "Modulation of angiogenesis-related protein synthesis by valproic acid" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 316, no. 3, 9 April 2004 (2004-04-09), pages 693-697, XP004495942 ISSN: 0006-291X abstract	1-30,35, 39-51
P,Y	----- SASAKAWA YUKA ET AL: "Antitumor efficacy of FK228, a novel histone deacetylase inhibitor, depends on the effect on expression of angiogenesis factors." BIOCHEMICAL PHARMACOLOGY. 15 SEP 2003, vol. 66, no. 6, 15 September 2003 (2003-09-15), pages 897-906, XP002278085 ISSN: 0006-2952 abstract	1-30,35, 39-51
P,Y	----- NAM NGUYEN-HAI ET AL: "Current targets for anticancer drug discovery." CURRENT DRUG TARGETS. FEB 2003, vol. 4, no. 2, February 2003 (2003-02), pages 159-179, XP0009029986 ISSN: 1389-4501 table 2 page 166, column 2, paragraph 1 page 173, column 1, last paragraph figure 11 page 175, column 1, last paragraph	1-30,35, 39-51
P,Y	----- WO 03/059354 A (KLUENDER HAROLD C E ; DUMAS JACQUES (US); ADAMS PAUL E (US); BAYER AG) 24 July 2003 (2003-07-24) page 80, line 15 - line 16 table 1 -----	1-30,35, 39-51

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/14071

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/090346 A (NOVARTIS ERFIND VERWALT GMBH ; MANLEY PAUL WILLIAM (CH); NOVARTIS AG ()) 14 November 2002 (2002-11-14) page 2, paragraph 3 page 3, paragraph 2 page 3, last paragraph - page 15, paragraph 2 page 19, last paragraph - page 20, paragraph 1 page 20, paragraph 2 page 20, last paragraph - page 21, paragraph 1	1-30,35, 39-51
Y	----- EP 0 847 992 A (MITSUI CHEMICALS INC) 17 June 1998 (1998-06-17) cited in the application page 5, line 17 - page 41, line 40 page 45, line 50 - page 46, line 2 claims 14-17	1-30,35, 39-51
Y	----- KIM M S ET AL: "Histone deacetylases induce angiogenesis by negative regulation of tumor suppressor genes." NATURE MEDICINE. APR 2001, vol. 7, no. 4, April 2001 (2001-04), pages 437-443, XP002278083 ISSN: 1078-8956 abstract	1-30,35, 39-51
Y	----- DEROANNE CHRISTOPHE F ET AL: "Histone deacetylases inhibitors as anti-angiogenic agents altering vascular endothelial growth factor signaling." ONCOGENE. 17 JAN 2002, vol. 21, no. 3, 17 January 2002 (2002-01-17), pages 427-436, XP002278084 ISSN: 0950-9232 abstract	1-30,35, 39-51
P,X	----- WO 03/022282 A (NOVARTIS PHARMA GMBH ; NOVARTIS AG (CH); WOOD JEANETTE MARJORIE (CH);) 20 March 2003 (2003-03-20) claims 6,12 page 4, paragraph 5 page 5, paragraph 2 page 7, paragraph 3 page 8, paragraph 3 - page 9, paragraph 2 page 2, paragraph 4	1-30,35, 39-51
P,Y	----- WO 03/028711 A (NOVARTIS PHARMA GMBH ; NOVARTIS AG (CH); DANA FARBER CANCER INST INC ()) 10 April 2003 (2003-04-10) page 1, paragraph 3 claim 2	1-30,35, 39-51

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/14071

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 42-44 and 49-51 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 31-34, 36-38
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 42-44 and 49-51 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 31-34, 36-38

Present claims 31-34 relate to combinations of two ingredients, the second of which is defined by reference to a desirable characteristic or property, namely its internal coordinates. This definition is considered unclear, *inter alia* given that it does not allow any meaningful comparison with the state of the art, and therefore any search, since the latter does not normally disclose such a property. These claims so lack clarity in the sense of Art 6 PCT that no search has been carried out. The same applies to claims 35, 39 and 40 as far as they refer to compounds of Formula IIa).

Present claims 36-38 refer to retine acid. It is not clear at all what this compound is supposed to be since it has not been possible to retrieve it from any database. The search of these claims has therefore not been possible.

Claims 41-50 have only been partially searched: not searched is their subject-matter as far as it refers to compounds of Formula IIa) or to claims 36-38.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/14071

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